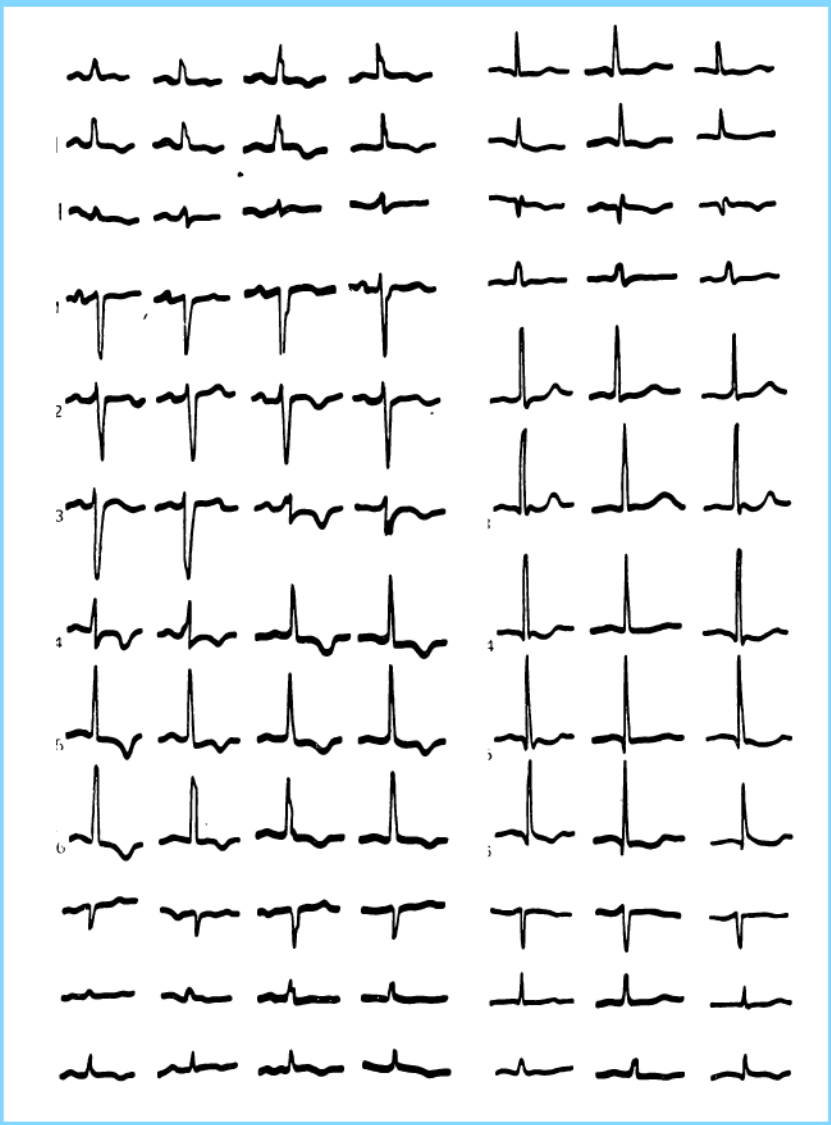
MYOCARDIAL INFARCTION

A. V. VINOGRADOV, A. M. VIKHERT, Z. Z. DOROFEEVA,
E. I. CHAZOV



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MYOCARDIAL INFARCTION

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PREFACE

The life of society and the need for safeguarding the health of the population continuously impose new problems on medical science. In the past they were most commonly 'diseases of the age' (cholera, plague, tuberculosis and rheumatism) which attracted the attention not only of physicians. They were usually characterized by high incidence, difficulty of diagnosis and treatment, and tragic consequences. The development of civilization and the achievements of medical science have pushed these diseases into the background.

One of the acutest problems today is undoubtedly myocardial infarction. As late as 50 years ago physicians seldom encountered this form of pathology and usually described it as casuistics. Only in 1910 did V. P. Obraztsov and N. D. Strazhesko in Russia and in 1911 J. B. Herrick in the USA gave a classical description of the clinical picture of myocardial infarction. Now not only physicians, but also broad sections of the population know about myocardial infarction because this disease occurs more often with each passing year. Suffice it to say that more than 400 000 people die annually of myocardial infarction in the USA. According to epidemiological studies, carried out by the Institute of Cardiology of the USSR Academy of Medical Sciences, in Moscow, for example, an average of three out of every 1000 men past 40 years of age are annually affected by myocardial infarction. We encounter this disease much more often in seemingly healthy young people. The youngest of our patients who died of myocardial infarction was a man 24 years old. Mortality is still high. The striving of researchers to ascertain the causes and mechanisms, and the complications of myocardial infarction, and to find the new and better methods of diagnosing and treating this disease is therefore quite natural.

The authors of this monograph have for many years concerned themselves with the problem of myocardial infarction in its various aspects. Several experimental and clinical studies have been published in Soviet and foreign journals. A. L. Myasnikov, our teacher, had suggested that we unify and summarize

the results of our studies. Every passing year, however, brought us new information, we wanted to supplement the book with something new, and A. L. Myasnikov's suggestion was carried into effect only five years after his death.

In our monograph we endeavoured to elucidate the problem of myocardial infarction fully enough from the point of view of its incidence and the mechanisms of its development, and also from the clinical standpoint, by dealing in particular detail with the modern methods of treatment. We wanted to describe myocardial infarction not separately as a nosological entity, but in close connection with various diseases of the heart and vessels. The solution of the problems connected with myocardial infarction probably reflects, like a mirror, all the problems of modern cardiology, since the problem of myocardial infarction is closely connected with those of atherosclerosis, heart failure, disturbances in the rhythm, etc. to say nothing about the methods of treatment which have a bearing not only on cases of myocardial infarction, but also on a number of other diseases of the heart and vessels. Such problems as fibrinolytic and anticoagulation therapy, as well as treatment of disturbances in cardiac rhythm and of heart failure, are the problems of cardiology of the day.

Objective evaluation of the facts constitutes the most difficult part of writing a monograph. We tried, as far as possible, to deal critically with our findings in various aspects of epidemiology, treatment, etc.

Despite the certain achievements of medicine the problem of myocardial infarction still presents many difficulties to the medical practitioner.

If this monograph helps the practitioner orient his actions in the problem of myocardial infarction more appropriately and to find a correct way in solving problems of cardiovascular pathology, we shall feel that our work was not in vain.

E. I. Chazov

1

PATHOLOGICAL ANATOMY

General Information

Atherosclerosis of the coronary arteries, ischaemic heart disease in all its manifestations, is a disease of the age and the problem number one for humanity. Myasnikov, one of the eminent Soviet scientists, pointed out in his monograph: 'Hypertensive vascular disease, atherosclerosis, and coronary failure associated with them form the grim triad of diseases which affect modern man to a greatest extent... . It is precisely these diseases that take a pall of millions of lives and hinder people from working and living in the prime of their life.' In its incidence, the number of patients and resultant invalidism and mortality myocardial infarction in a number of countries holds the first place overstripping even malignant tumours.

There are no exhaustive statistical data on myocardial infarction since this problem has grown particularly acute during the last two or three decades, and thorough epidemiological studies began to be conducted only ten to fifteen years ago, and not in all countries by far. A certain idea on the acuteness of the problem is given by the information on mortality from cardiovascular diseases per 100 000 population published by the World Health Organization in 1958. Some of the findings taken from this study are cited below.

The USA lead in the death rate of men between 50 and 54 years of age (467 whites and 441 Negroes) and are followed by Finland (405) and Canada (404); at the age of 60-64 the death rate is 1157 in the USA, 1080 in Scotland, 1029 in Finland and 1016 in Canada. The lowest mortality in both the above age groups is in Japan (70 and 187 respectively), Portugal (80 and 308) and Hungary (151 and 439).

We shall not dwell in detail on epidemiological research however. We have cited the foregoing data merely to illustrate the im-

portance of the problem of coronary atherosclerosis to the population of most of the developed countries. The high mortality of the population from atherosclerotic heart diseases is due primarily to the high mortality from myocardial infarction in the early or acute period, i.e. during the first days of the disease, as well as in more remote periods.

The information on hospital mortality during the early period of myocardial infarction cited by various authors is subject to wide variations. This is due to many factors which cannot always be accounted for, namely, the country and its organization of health service, the severity of the cases admitted to hospitals, the periods of hospitalization, the method of treatment, and the period to which the given data belong.

Lukomsky (1940), for example, cites hospital mortality of 9.8 per cent (8 of 85 patients admitted), while Zolotova-Kostomarova (1950) mentions 32 per cent. Even the data of the same author may differ considerably in different years. According to Lukomsky and Tareev (1958), in particular, hospital mortality in 1957 amounted to 20 per cent. Inverse proportions were observed by Glazova (1956): 26.9 per cent during 1929-1944 and only 8.7 per cent in 1954. Extremely high figures are cited by Hochrein (1945) (58.6 per cent) and Eckerström (1951), whereas Bear *et al.* (1951) and Smith (1953) mention very low figures—8.8 per cent. According to the summary data of Berinskaya *et al.* (1958), hospital mortality was higher before 1945 when it averaged 30 per cent (the data of Soviet authors) and 35.5 per cent (of foreign authors). During the following decade it was observed to decrease to 17.4 and 28.7 per cent, respectively.

According to the data of the Institute of Cardiology (USSR Academy of Medical Sciences), hospital mortality amounted to 315 per 1000 myocardial infarction patients in 1966, 241 in 1967, 202 in 1968 and 205 in 1969, i.e. in four years it decreased 34.1 per cent.

Many authors are inclined to explain the decrease in hospital mortality during the last decade by extensive use of anticoagulants. A decrease in mortality from 20 to 7.2 per cent of the patients treated with anticoagulants is noted by Lukomsky and Tareev (1957), while Yasakova (1959) mentions a decrease from 19.5 per cent among untreated patients to 2.8 per cent in the group of patients treated with anticoagulants. According to Novikova (1965), hospital mortality is 80 per cent lower among the patients treated with anticoagulants than among those not treated. The decrease in mortality was due to that in the number of thromboembolisms and rupture of the myocardium. Many authors (Golovash, 1956; Manson and Fullerton, 1956; Kushelevsky, 1958, and others) note a favourable effect of anticoagulation therapy.

Organization of specialized aid in a number of Soviet cities, especially during the very first hours and days when the patients are in the greatest danger, played an incontestable role in decreasing mortality. Lang (1957) holds that 50 per cent of myocardial infar-

ction patients die during the first eight days. According to V. N. Vinogradov (1965), 27.4 per cent died during the first two days. Moiseev (1965) holds that the largest number of fatal cases—17.3 per cent occurs in the first day and 56 per cent in the first week. Close figures are mentioned by Berinskaya *et al.* (1958): 18.2 per cent in the first day and a decrease to 10.8 per cent during the following two days. According to Glazova (1949), 35 per cent of the fatal cases occur during the first three days, 17 per cent during the first two weeks, i.e. 52 per cent of fatal results were observed during the first two weeks. High figures pertaining to this period are cited by Bean (1938) (73.8 per cent), Eckerström (1951) (82.3 per cent) and Raevskaya (1955) (64.6 per cent). At the Institute of Cardiology 33 per cent of patients died in the first day, 67.1 per cent in the first week, and the rest in the course of one month after the onset of the disease. Thus it is perfectly clear that precisely the first days are the most dangerous to myocardial infarction patients.

The incidence of myocardial infarction, according to autopsy data, may vary widely depending on the type of the medical institution, the periods of patients' hospitalization and the share of other forms of hospital mortality, but in the large does not generally exceed 5-10 per cent of the autopsies; 4.9 per cent—Barnes and Ball (1932); 7.8 per cent—McCain *et al.* (1950); 4.1 per cent—Benson *et al.* (1958). At the Institute of Cardiology, however, this percentage is very high (22.7) which is explained by the general contingent of patients admitted to the Institute, whereas in the hospitals affiliated with Institute's laboratory of pathology it amounts to 15.5 per cent. The latter figure possibly reflects, on the one hand, the increased incidence of myocardial infarction and more complete hospitalization of these patients, and on the other, a decrease in the other forms of hospital mortality in virtue of which the share of all fatal results of myocardial infarction relatively increases.

Among the infarctions diagnosed during autopsy a fairly important role is played by 'mute' infarctions, both recent and remote, but undiscovered during the patients' lifetime. Thus Gould and Cowley (1958) point out that of the 452 cases of old infarctions in 39 per cent the anamneses contained no clinical indications of the disease. In the Framingham study[1]) the number of clinically undiagnosed infarctions amounted to 21 per cent (15 observations of the 73). Asspenström noted 20 per cent of undiagnosed fresh infarctions in 138 observations. According to this author, 'mute' infarctions most commonly occur in old people, diabetics and in the presence of simultaneous cerebral affections. Symptomless infarctions in old age are also mentioned by Smoliyannikov (1958) and Naddachina (1961).

The prevalence of men among myocardial infarction patients,

[1]) See Chapter 3.

especially in younger age groups, is a generally known fact. According to Kofanov (1949), during 1939 to 1946 the Sklifosovsky First Aid Institute admitted 549 men and 93 women (a 6 : 1 ratio) with myocardial infarction. The larger number of men among the patients is, naturally, reflected in autopsy data.

In the materials of Shamesova (1956) the men to women ratio was 111 : 30; Berinskaya *et al.* (1958) 62 and 38 per cent; Allison *et al.* (1963) 238 : 192; Strukov *et al.* (1967) 266 : 148; Goodal *et al.* (1960) 63 and 37 per cent, respectively.

Among 500 myocardial infarction patients Barnes and Ball (1932) observed 4 : 1 men to women ratio; Backer and Willings (1938) 7 : 1; Chambers (1946) 3 : 1, and Master and Dack (1949) 3.4 : 1.0. These small variations of infarction incidence among men and women are, of course, in some measure fortuitous, but the more frequent affection of young men may be considered an incontestable fact.

A detailed analysis of decades of life shows that the prevalence of men is mainly accounted for by the younger age groups (under 50 years), while later the difference largely disappears. According to Berinskaya *et al.* (1958), from 41 to 50 years of age the ratio was 5.1 : 1, from 51 to 60 it was 2 : 1, from 61 to 70—1.5 : 1, and past 70 it was only 0.9 : 1.

Analysing the materials of the Mayo Clinic for the period from 1935 to 1945 Underdahl and Smith (1947) observed among 95 000 patients with various diseases only 27 women under 40 years of age with ischaemic heart disease, myocardial infarction having been diagnosed only in seven cases.

According to our own data, 13 men and not a single woman died of myocardial infarction under 50 years of age. At the age of 50-59 years this ratio was 2.6 : 1 (68 men and 25 women), while during the subsequent decades of life these figures were about equal (123 men and 108 women at the age of 60-69 years) or the ratio was reversed (only 59 men and 88 women died at 70 to 79 years of age). Analogous or close ratios of male and female mortality due to coronary insufficiency and myocardial infarction were found by a study of autopsy materials collected in nine Soviet cities (Riga, Tallinn, Tartu, Kharkov, Yalta, Moscow, Irkutsk, Kaunas and Ryazan) in accordance with the programme of the Centre for Studying the Epidemiology of Atherosclerosis in the Soviet Union: 78 per cent of cases were men and 22 per cent women. The number of women appreciably increases in the older age groups. Whereas the men to women ratio under the age of 40 was 9 : 1, at the ages of 40-49 and 50-59 it is already about 5 : 1, and at the age of 60-69 it was 2 : 1. This 'lagging' of younger women is apparently due to the fact that coronary atherosclerosis, especially its severe stenotic forms, develops in women 10 to 15 years later than in men, the ratios becoming equalized only during older age periods.

Recently there has apparently been a tendency toward an in-

crease in the incidence of myocardial infarction among women. According to the summary literary data compiled by Berinskaya *et al.* (1958), until 1945 there were 82.2 per cent of cases of myocardial infarction among men and 17.8 per cent among women, whereas in the period from 1946 to 1956 men accounted for 73.9 per cent and women for 26.1 per cent of the disease.

The most threatening age for men is between 50 and 59 years and the two following decades. According to the data of the Institute of Cardiology, during these years there are 90.2 per cent of fatal outcomes from myocardial infarction. In women fatal outcomes occur one decade later, 83.7 per cent of fatal cases taking place between 60 and 79 years of age. According to Bean (1938), 10 per cent of myocardial infarctions occur between 40 and 49 years of age, 25 per cent between 50 and 59, 35 per cent between 60 and 69, and the remaining 30 per cent during other age periods.

At the same time myocardial infarction in young people is no longer a rare occurrence. Literature contains numerous descriptions of individual cases and an analysis of many observations. Of the 221 cases of coronary occlusion studied by Reitmann *et al.* (1942) 34 were patients under 40 years of age and four under 20. Miller and Woods (1943) cite eleven cases taken from the literature and describe one of their own observations of coronary death of young persons (two of the 12 patients were women; syphilis was absent in all cases). In 1946 Newman analysed 50 analogous cases of 35-year-old persons (one woman was 28 years old). In 39 cases the diagnosis was confirmed by autopsy. In 17 cases the left coronary artery was affected by atherosclerosis, in five cases—the right, and in 16 cases—both; in 29 cases there was no thrombosis. Myocardial infarction has been described in 16-year-old boys (Douglas and Marienberg, 1949; Syme and Allan, 1951) and in 16-19-year-old girls (Evans and Graybiel, 1948) and 19-year-old boys (Hunter and Insall, 1959). The largest number of observations is cited by Yater *et al.* (1948); they analyse 866 cases of coronary disease at the age of 18-39 years. In 450 cases the diagnosis was confirmed by autopsy.

Data on the increasing incidence of the ischaemic heart disease in young people are cited in the study of Saphir *et al.* (1956) who collected during 34 years 2165 cases of death from myocardial infarction (1403 were males and 762 females). Of this number the group under 50 years of age accounted for 7.3 per cent during 1920 to 1929 and for 11.5 per cent during 1950 to 1953. In the opinion of Adlersberg and Zak (1952) and Gertler and While (1954), the peculiarities of myocardial infarction in young people was that it was encountered among those whose relatives also often suffered from myocardial infarctions and other heart diseases. According to Gertler *et al.* (1954), myocardial infarction in the families of young patients occurred four times as often. Hypertension, gout, diseases of the gall bladder and gastric ulcer were often observed. According to Adlersberg and Zak (1952), the patients most frequently had hyper-

cholesterolaemia and less frequently diabetes. Most of them were smokers. Autopsy of the young more often showed hypertrophy of the heart (500 g and more) and a disproportion between severe coronary atherosclerosis and insignificant affection of other vessels.

The development of the disease is frequently preceded by excessive physical exertion (Syme and Allan, 1951; Gertler *et al.*, 1959).

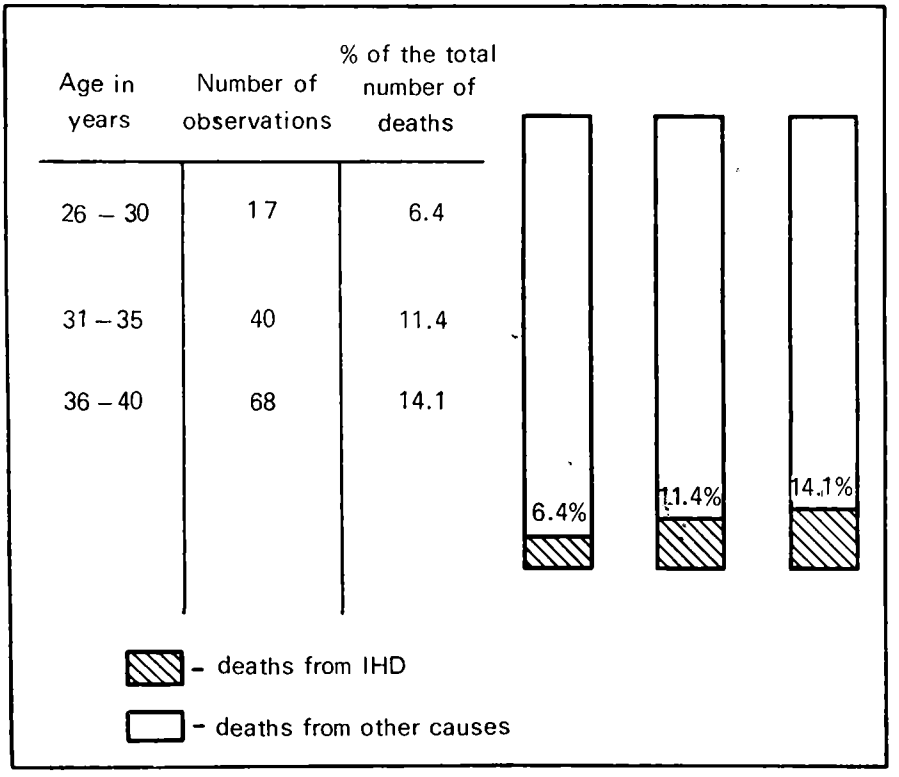

Fig. 1. Incidence of mortality from acute coronary failure and myocardial infarction among young people

Clawson (1941) and Naddachina (1961) emphasize the important role of hypertension in the development of coronary death. Uehlinger (1967) also regards hypertension, various metabolic disturbances and physical overexertion as factors which intensify coronary atherosclerosis and, consequently, foster the development of the ischaemic heart disease. At an early age he attaches particular importance to inflammatory changes in the coronary arteries of a type of endarteritis whose aetiology is unclear. Bredt (1949) holds similar views. He believes coronary sclerosis under 45 years of age to be a special disease of the type of endarteritis obliterans which must be distinguished from atherosclerosis in its usual conception. It is difficult to agree with this. We examined the main branches of the coronary arteries in 188 fatal cases of acute coronary insufficiency and myocardial infarction in persons under 40 years of age and did not find any inflammatory changes in a single case. Non-

specific aortitis with affection of the vessels arising from the aorta, including the coronary vessels, developed only in one 29-year-old man.

As our studies have shown (Vikhert and Matova, 1966), death from acute coronary insufficiency and myocardial infarction at an early age plays, despite its seemingly rare occurrence, an important part in the total structure of mortality at this age period. The reason for it is that the number of other forms of death, e.g. from infectious diseases, has now sharply decreased, while malignant tumours in young people occur relatively rarely. At 26-30

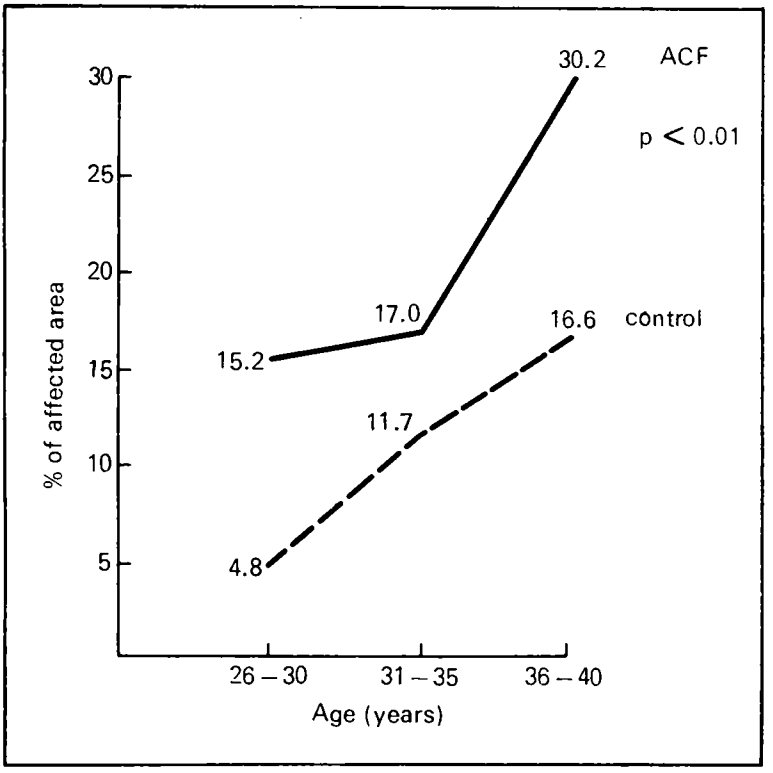

Fig. 2. Atherosclerosis of the descending branch of the left coronary artery in practically healthy people and in young people who died of myocardial infarction (ACF—acute coronary failure)

years of age ischaemic heart disease accounts for 6.4 per cent of fatal cases, at 31-35 years for 11.4 per cent and at 36-40 years for 14.1 per cent (Fig. 1). The fact that 58.8 per cent fatal cases were manual workers, 22.8 per cent were people with a higher education (engineers, physicians, etc.) and 18.4 per cent were persons of other occupations also deserves attention. It is necessary to consider the occupational structure of the population in which manual workers constitute the majority. These figures do not reflect the morbidity of the different occupational groups, but it cannot be said, however, that the main victims of coronary insufficiency at an early age are brain workers.

The degree of coronary atherosclerosis in patients who died of coronary insufficiency under 40 years of age exceeded that in persons who died of accidental causes (mainly traumas) (Fig. 2). At the same time severe stenotic atherosclerosis was found only in 10.5 per cent of the cases, although this was five times as frequent as in the control group. The fact that one of the main trunks of the coronary arteries was weakly developed in 34.5 per cent of the cases also deserves attention. The increased weight of the heart (more than 400 g) was observed in 36 per cent of cases. It is noteworthy that under 40 years of age sudden death[1]) occurs much more frequently, in 96 per cent of fatal cases of acute coronary insufficiency, whereas between 60 and 69 years of age it occurs only in 61.9 per cent of cases. This may be accounted, first, by a weakly developed collateral circulation in young people (see below) and, second, perhaps by the fact that young people do not take medical advice on the appearance of the first symptoms of the disease. The latter supposition is corroborated by the fact that 37 per cent of the people who suddenly died under the age of 40 years had a macroscopically formed myocardial infarction, i.e. the disease was already at least of 24 hours' standing.

The Blood Supply to the Myocardium

Since myocardial infarction in the overwhelming majority of cases is associated with a total cessation of, or sharp decrease in, the blood flow through the coronary vessels, it is necessary, in order to understand its aetiology and pathogenesis, to have a clear idea of cardiac blood circulation, the anatomy of the coronary arteries, the zones they supply with blood, the existence of anastomoses between the main branches of the coronary vessels, the possibility of collateral blood circulation and the conditions favouring its development.

The heart is supplied with blood through two main vessels—the right and left coronary arteries which arise from the aorta immediately above the semilunar valves. The left coronary artery arises from the left posterior aortic sinus (Valsalva's sinus), runs downward to the anterior longitudinal groove, leaving the pulmonary artery on the right and the left atrium with auricle surrounded by fatty tissue, which usually covers it, on the left. It is a wide, but short trunk usually not longer than 10 or 11 mm. The left coronary artery divides into two, three and, in rare cases, into four branches of which the most important to pathology are the anterior descending and circumflex branches or arteries.

The anterior descending artery is a direct continuation of the left coronary artery. It runs along the anterior longitudinal groove

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[1]) We regarded death as sudden when it occurred in seemingly healthy people or during the first six hours after appearance of the symptoms of the disease.

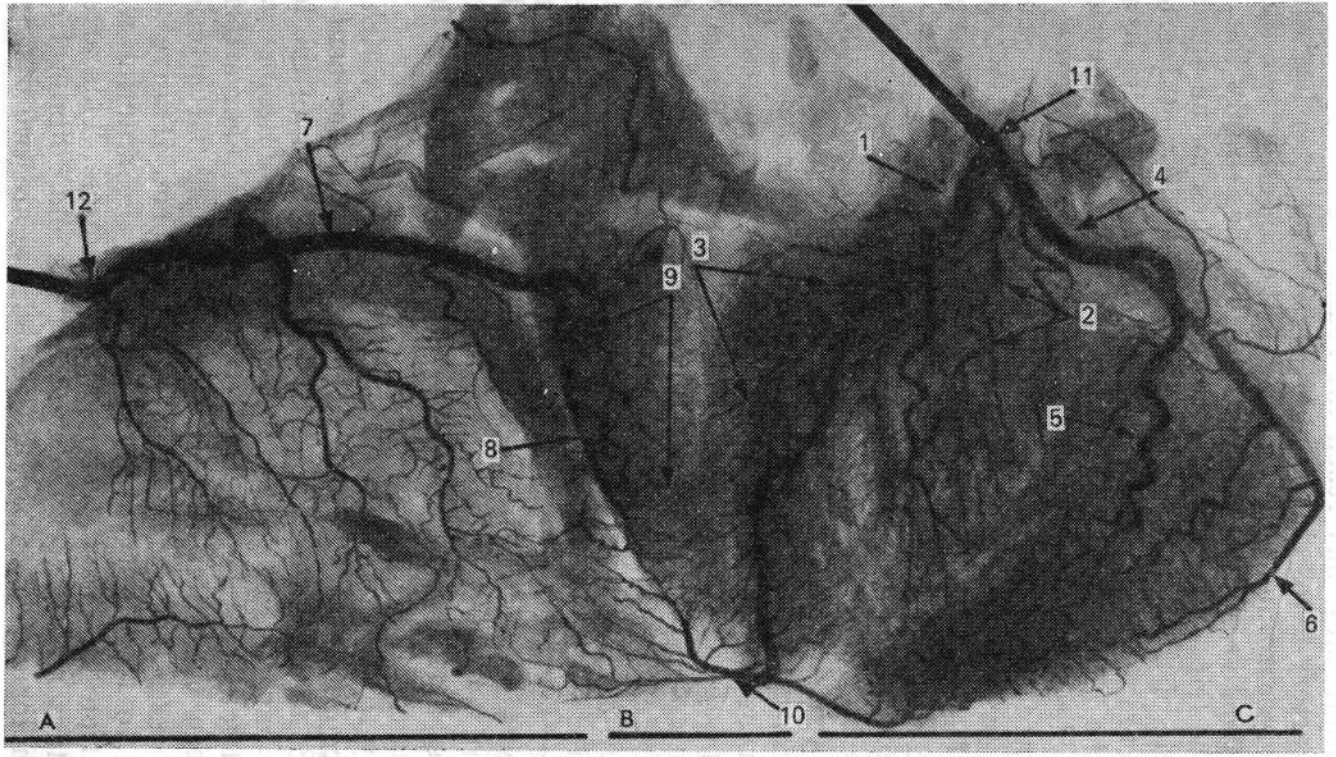

Fig. 3. Radiograph of an open heart after filling the coronary arteries with a contrast medium

1, *10*—anterior descending artery; *2*—diagonal arteries; *3*—septal branches supplying the anterior parts of the septum; *4*—circumflex artery; *5*—artery of the blunt edge; *6*—posterior descending artery; *7*—right coronary artery; *8*—posterior descending artery (from the reservoir of the right coronary artery); *9*—septal branches supplying the posterior parts of the septum; *11*—ostium of the left coronary artery; *12*—ostium of the right coronary artery. *A*—open wall of the right ventricle; incision made along the anterior edge of the interventricular septum (from top to bottom); *B*—interventricular septum; *C*—open wall of the left ventricle; incision made along the posterior edge of the interventricular septum (from top to bottom)

of the heart to the area of the cardiac apex, usually reaches it, sometimes curves over it and runs to the posterior surface of the heart (Fig. 3). Several smaller lateral branches arise at an acute angle from the descending artery and run along the anterior surface of the left ventricle where they may reach the rounded border; moreover, the descending artery gives rise to numerous septal branches which perforate the myocardium and ramify in the anterior two-thirds of the interventricular septum. The lateral branches supply the anterior wall of the left ventricle and give off branches to the anterior papillary muscle of the left ventricle. The superior septal artery gives off a small branch to the anterior wall of the right ventricle and sometimes to the anterior papillary muscle of the right ventricle.

The anterior descending branch lies all along its course on the myocardium, sometimes immersing in it and forming muscular bridges one or two centimetres long. Along the rest of its course its anterior surface is covered with fatty cellular tissue of the epicardium.

The circumflex artery or, as it also called, the circumflex branch of the left coronary artery, usually arises from the latter in the very beginning (the first 0.5 to 2 cm) almost at a right angle, runs in the transverse groove, reaches the rounded border (see Fig. 3) of the heart, curves over it (here it gives off the left marginal artery), extends to the posterior wall of the left ventricle, sometimes reaches the posterior interventricular groove and runs to the apex as the posterior descending artery. Numerous branches arise from it and run to the anterior and posterior papillary muscles, and the anterior and posterior walls of the left ventricle (see Fig. 3). The size and extent of artery are very variable. Sometimes it ends in the region of the rounded border, in other cases it continues along this border downward as the marginal artery without extending to the posterior surface (Fig. 4, *6*). It also gives off one of the arteries that supplies the sino-atrial node.

It is necessary to note the less constant diagonal artery, which is encountered, according to Crainicianu (1913), in 60 per cent of cases (see Fig. 3, *4*, *6*). It arises from the site of division of the left coronary artery and runs obliquely downward on the anterior wall of the left ventricle, first between the two aforedescribed arteries and then between the anterior descending and marginal arteries, in a number of cases forming anastomoses with them. It gives off a few branches to the interventricular septum, the anterior wall of the left ventricle and its anterior papillary muscle. This artery plays an important role in forming anastomoses and collateral circulation in pathological cases. In rare cases there are two diagonal arteries (see Fig. 3).

The right coronary artery begins at the anterior Valsalva's sinus. At first it runs deep in the fatty tissue to the right of the pulmonary artery, curves around the heart along the right atrioventricular groove, extends to the posterior wall, reaches the posterior longitu-

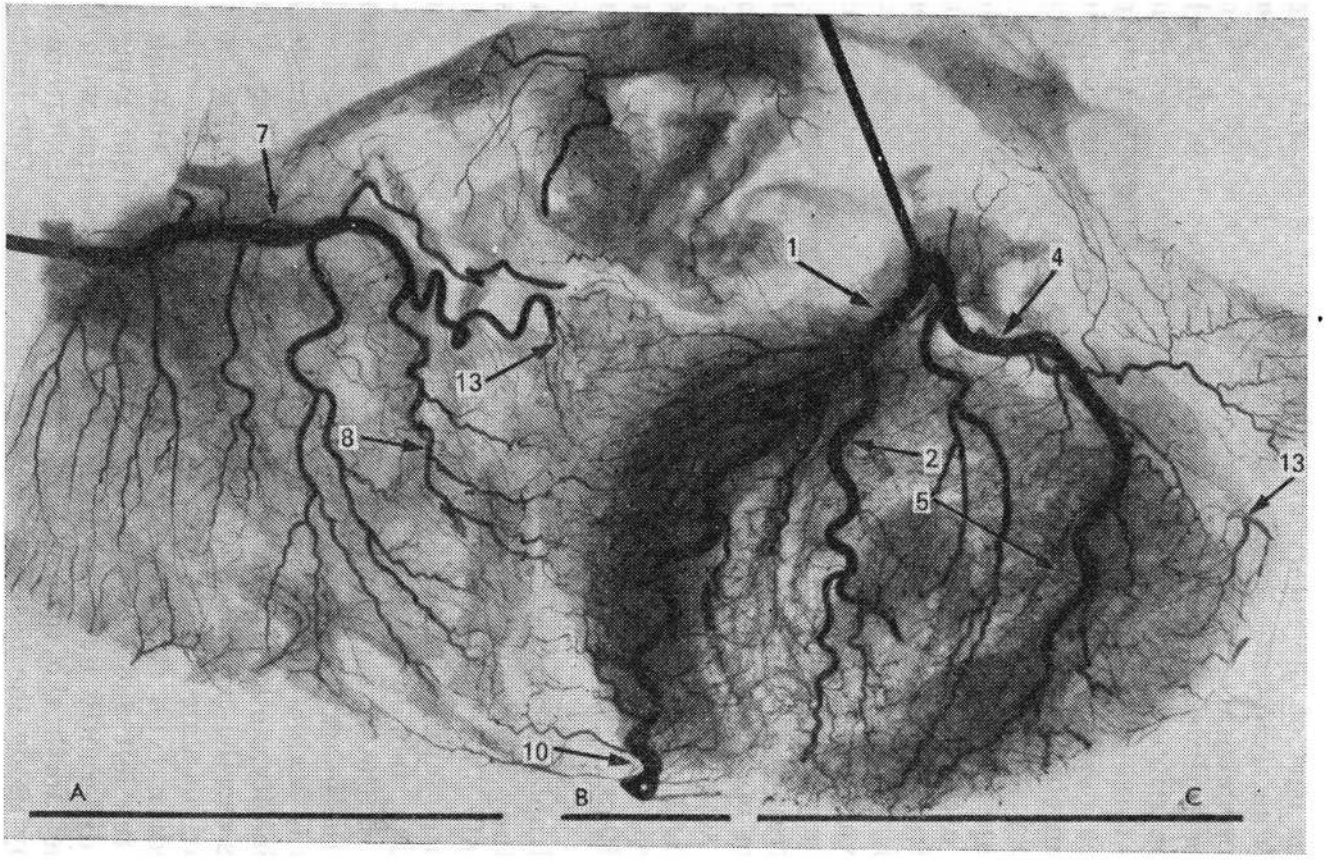

Fig. 4. The left circumflex artery (*4*) terminates as an artery of the blunt edge (*5*). A branch of the coronary artery (*13*) extends to the posterior surface of the left ventricle and participates in supplying it with blood. The branch was incised in opening of the heart. The region of the incision is shown by an arrow (*13*). Other designations are as in Fig. 3

dinal groove and then, as a descending branch, runs down to the apex of the heart (see Fig. 3). The artery gives off one or two branches to the anterior wall of the right ventricle (right marginal artery), partly to the anterior part of the septum, both papillary muscles of the right ventricle, the posterior wall of the right ventricle and the posterior part of the interventricular septum; a second branch also arises from it and runs to the sino-atrial node. In certain cases the right coronary artery gives off a posterior diagonal branch on the posterior surface of the right ventricle. Now and then the right artery, after giving off the posterior descending branch, continues and reaches the blunt border of the heart, participating in supplying blood to the posterior wall of the left ventricle and its posterior papillary muscle. In this case the circumflex branch of the left coronary artery is usually weakly developed.

It also happens relatively frequently that there are two posterior descending arteries, one arising from the right coronary artery and the other from the circumflex branch of the left coronary artery (see Fig. 3).

Various variants of distribution and extension of each of the main trunks of the coronary arteries and their branches and, consequently, various correlations of their reservoirs of the blood supply to the myocardium may be observed. These variants or types of the normal blood supply are set forth in detail in a number of studies (Gross, 1921; Lisitsin, 1927; Schlesinger, 1938; Ravin and Geever, 1946; Tolgskaya, 1946; Sokolov, 1947; Ariev, 1949; Kuzmina-Pregradova, 1949; Ognev *et al.*, 1954; Schoenmeckers and Vieten, 1954).

We shall not analyse in detail the views of various authors since a special study of the coronary circulation, as such, is not our task. We shall only point that we consider it the most appropriate to distinguish three main types of blood supply to the myocardium, namely, median, left and right. This division is mainly based on the variations of the blood supply to the posterior or diaphragmatic surface of the heart, since the blood supply to the anterior and lateral parts is stable enough and not subject to appreciable deviations. As Smoliyannikov and Naddachina (1963) justly noted, different authors ascribe the blood circulation to a particular type on the basis of various signs. There are no universally recognized criteria. In the median type the blood is supplied uniformly through the system of the left and right arteries. The left and right types are conceived differently by different authors. In connection with this we shall set forth the information taken from the literature and obtained by us on the basis of angiographic studies of 50 hearts of people under 40 years of age who died from accidental causes, did not have during their lifetime (as far as it was possible to ascertain) any signs of coronary insufficiency or, on autopsy, any fresh (infarcts) or former (postinfarction scars, cardiosclerosis) manifestations of coronary insufficiency.

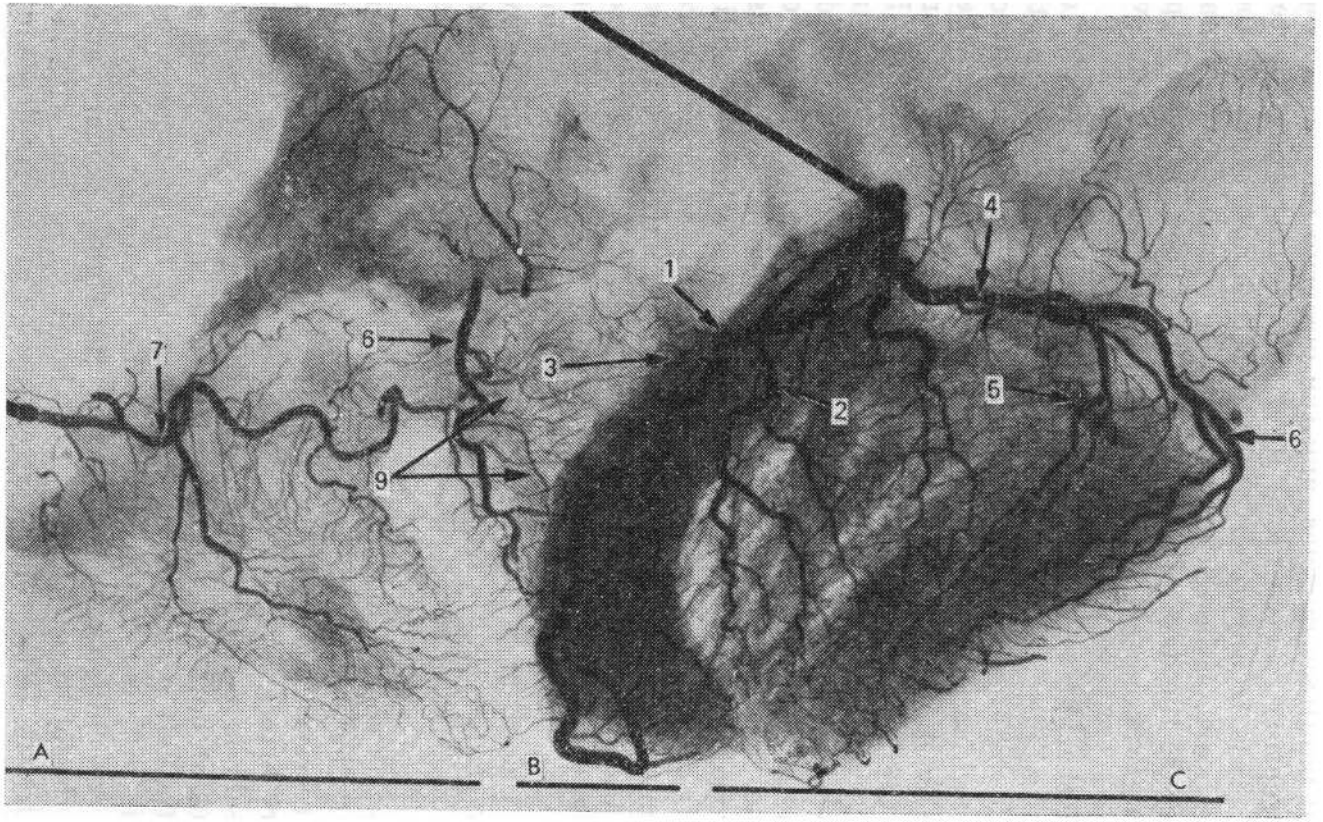

Fig. 5. Left type of coronary blood supply. The anterior descending (*1*) and circumflex (*4*) arteries are well developed, the right coronary artery (*7*) is poorly developed. The posterior descending artery (*6*) supplies the posterior part of the septum (was incised at the edge of the heart in its opening from the right and is well seen in the region of the septum). Designations are as in Fig. 3

In cases of the median type all the three main coronary arteries are developed well and fairly uniformly. Blood is supplied to the whole left ventricle, including both papillary muscles, and to the anterior one-half to two-thirds of the interventricular septum, by the system of the left coronary artery. The right ventricle, including both right papillary muscles, and the posterior one-half to one-third of the septum receive blood from the right coronary artery (see Fig. 3). This is apparently the most common type of blood supply to the heart, although we cannot cite even its approximate frequency because the data of different authors vary between 23 per cent (Kuzmina-Pregradova, 1949) and 70 to 80 per cent (Kazakova, 1955).

In cases of the left type the blood is supplied to the whole left ventricle, the whole septum and partly the posterior wall of the right ventricle by the developed circumflex branch of the left coronary artery which reaches the posterior longitudinal groove where it terminates as the posterior descending artery, giving off some branches to the posterior surface of the right ventricle (Fig. 5).

The right type is observed in cases of the weakly developed circumflex branch which either terminates before reaching the blunt border or merges in the coronary artery of the blunt border without extending to the posterior surface of the left ventricle. In such cases the right coronary artery, after giving off the posterior descending artery, usually gives off several more branches to the posterior wall of the left ventricle. Moreover, the whole right ventricle, the posterior wall of the left ventricle, the posterior left papillary muscle and partly the apex of the heart receive blood from the right coronary artery (Fig. 6). This is one of the most frequent types of blood circulation. According to Schlesinger (1938), Ravin and Geever (1946), Ariev *et al.* (1949), Kuzmina-Pregradova (1949), and Smoliyannikov and Naddachina (1963), it occurs in 46 to 67 per cent of the cases.

There are some special features in the blood supply to the papillary muscles. The left anterior and right posterior papillary muscles usually receive blood wholly from the anterior descending and right coronary arteries, respectively. The blood supply to the right anterior muscle is usually mixed, i.e. this muscle receives blood from branches of both arteries, which is in a number of cases also observed in the left posterior papillary muscle. In most cases, however, blood is supplied to the latter by the circumflex artery and in a certain percentage of cases also by the right coronary artery.

In cases of the left type the apex of the heart is supplied with blood in the main by the left coronary artery, to be exact, its descending branch which often curves over the region of the apex and extends to the posterior surface (see Fig. 3, *4*, *5*). In case of the right type the right coronary artery (its posterior descending branch) may also curve over the region of the apex, but in the opposite direction, and extend to its anterior surface, providing a nearly complete flow

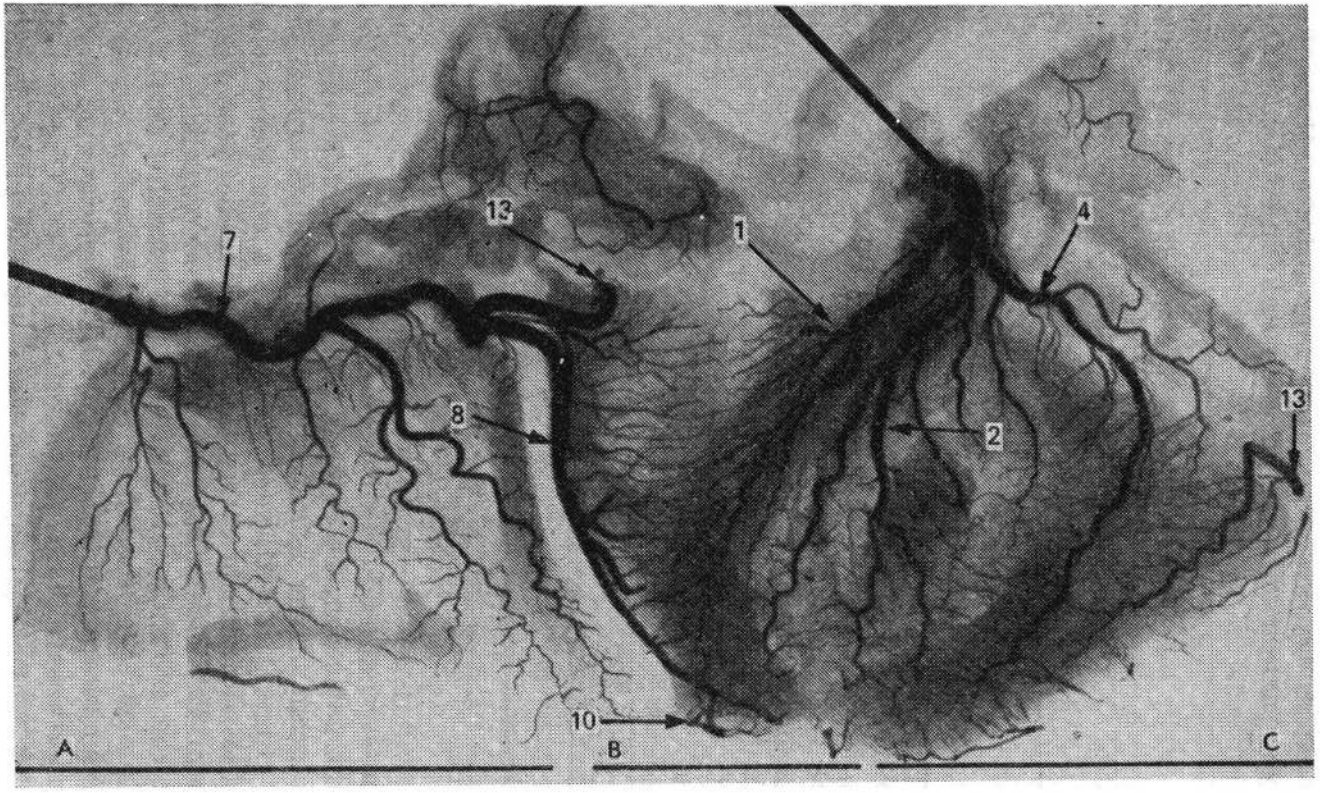

Fig. 6. Right type of coronary blood supply. Relatively small anterior descending artery (*1*), diagonal artery (*2*), circumflex artery (*4*), artery of the blunt edge (*5*). Right coronary artery (*7*) gives rise to strongly developed posterior descending artery (*8*) and continues as a branch (*13*) on the posterior surface of the left ventricle. In the region of the apex the posterior descending artery extends to the anterior surface of the left ventricle (*10*)

of blood to this region (see Fig. 6). Lastly, various correlations in supplying blood to the apex are possible by both aforesaid arteries, e.g. in the median type of circulation.

The myocardium is supplied with blood directly: (a) by the capillaries lying between muscle fibres which braid with them and receive blood from the system of coronary arteries through arterioles; (b) by a rich network of myocardial sinusoids; (c) by the

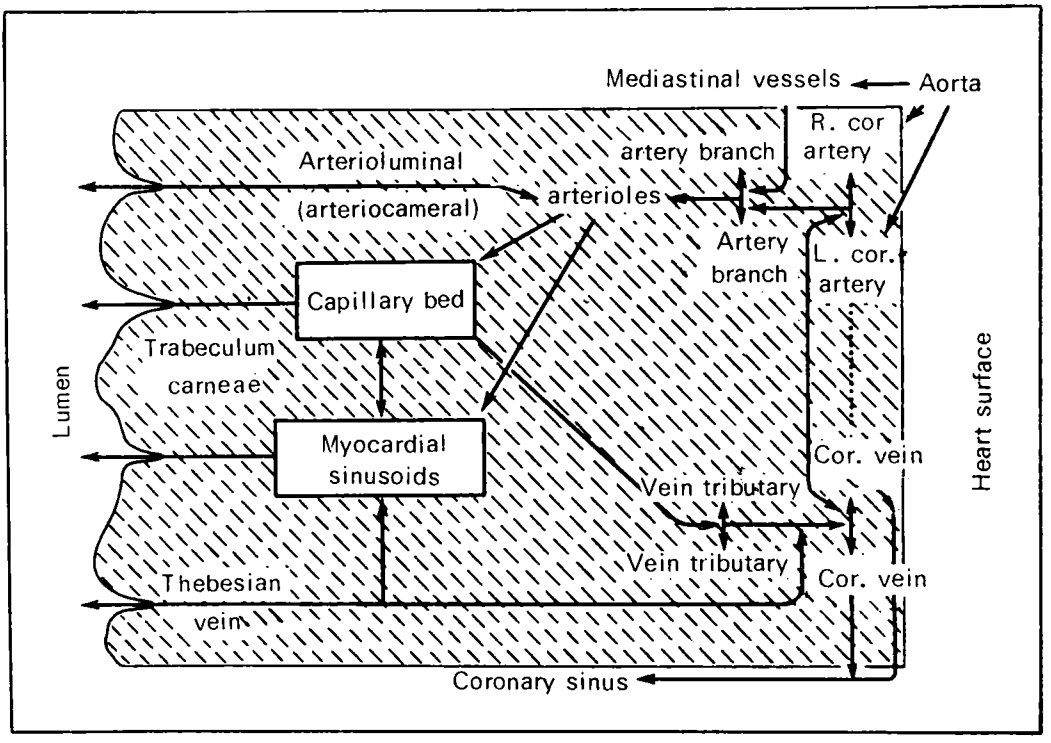

Fig. 7. Diagram of myocardial circulation (after Reginald E. B. Hudson)

vessels of Vieussens and Thebesius. The outflow takes place through the veins which gather in the coronary sinus. Hudson's study (1965) contains a diagram of the blood supply to the myocardium. From this diagram (Fig. 7) it follows that there is a communication between the capillaries and the sinusoids, as well as between the latter and the veins of Thebesius. Moreover, the blood may be discharged directly from the arterioles either into the ventricles or the veins.

The direction of the blood flow through Thebesian veins is not clear.The blood may apparently flow in both directions and,moreover, may change in pathological conditions (Ilinsky, 1952; Ozarai, 1956).

Provenza and Scherlis (1959) hold that the local blood circulation is regulated by a system of sphincters. They distinguish meta-arterioles, precapillaries and capillaries. The meta-arterioles are of the same calibre as capillaries, but in the wall to the outside of the endothelium have several muscle cells which play the role of sphincters that direct the blood flow. The precapillaries also have sphinc-

ters of two or three muscle cells at the point where they arise from arterioles or meta-arterioles. Lastly, the capillaries are mere tubules formed by endothelium. Contraction of the sphincters may deflect the blood flow to some region of the myocardium and thereby regulate the microcirculation. Moreover, these authors describe arteriovenous anastomoses which play the role of shunts that drain the blood directly from the arteries or arterioles into the venous system.

Cohnheim's (1881) opinion that there are no anastomoses between the branches of the coronary arteries now has no supporters. Intercoronary anastomoses undoubtedly exist and play an important role in coronary circulation, especially in pathological conditions (Fokht, 1901; Schpalteholz, 1924; Ivanov, 1932; Anichkov, 1939; Ravin and Geever, 1946; Tolgskaya, 1946; Prinzmetal *et al.*, 1948; Blumgart *et al.*, 1950; Schoenmackers, 1950; Zoll *et al.*, 1951; Kikaion, 1956; Paul *et al.*, 1957; Vastesaeger *et al.*, 1957; Pitt, 1959; Laurie and Woods, 1962; Smoliyannikov and Naddachina, 1963; Spain *et al.*, 1963).

Regrettably the different authors studied intercoronary anastomoses by entirely different methods. Some of them studied these anastomoses on corrosive preparations (e.g. Schpalteholz, 1924), others injected roentgen contrast media or mixtures, solutions of agar or gelatin with an addition of various proportions of some barium or lead salts, lead paints, etc., differing not only in the proportions of the ingredients, but also in viscosity, density and size of the particles. Still others used particles of various plastics, latex or glass beads 40 to 200 μ in diameter, the system of coronary vessels being filled under different pressures (70 to 150 mm Hg). Such great differences in the methods account for the considerable diversity of the results. Schpalteholz (1924) and Schoenmackers (1950) suggest that we distinguish, firstly, anastomoses between different arteries (intercoronary, e.g. between the right and the branches of the left coronary artery, the circumflex and anterior descending arteries) and, secondly, collaterals which interconnect branches of the selfsame artery and create by-passes as it were, e.g. between the branches of the anterior descending artery, arising from it at different levels. Anastomoses were studied in detail on corrosive preparations by Schpalteholz who established the existence of numerous anastomoses in the interventricular septum through the anterior and posterior septal arteries. These are, however, mainly anastomoses between arteries of the fourth or fifth order not exceeding 40 μ in diameter, i.e. precapillary arterioles and capillaries. On the other hand, anastomosis between larger branches occurs inconstantly and rarely. Giese and Müller-Monhnssen (1958) and Schoenmackers (1958) discovered precapillary anastomoses between the branches of the right and anterior descending arteries in the region of the interventricular septum and the apex, in the posterior wall of the left ventricle between the right coronary and circumflex arteries, and in the anterior wall of the left ventricle between the

anterior descending and left circumflex arteries. Their prevalent localization is intramyocardial; they are encountered less frequently in the subendocardial zone. Blumgart *et al.* (1950) have shown that there are more anastomoses in the hearts of persons affected with ischaemic disease, for which reason the occlusion of one of the main coronary arteries is not always accompanied by necroses in the myocardium. In normal hearts anastomoses have only been found in 10 to 20 per cent of cases, and of a small diameter at that. Their number and size, however, increase not only in coronary atherosclerosis, but also in valvular heart disease. Age and sex of themselves do not in any way affect the presence of anastomoses or the degree of their development. Zoll *et al.* (1951) studied 1050 hearts by means of the injection technique and roentgenography and arrived at the following conclusions:

1. In normal hearts anastomoses occur in 9 per cent of cases.
2. In persons affected with anaemia they are found in 39 per cent.
3. In occlusion of one or more branches their frequency amounts to 89-100 per cent, in stenosis to 11-63 per cent, depending on its degree.
4. In cases of pulmonary heart anastomoses occur in 73 per cent, in arterial hypertension in 26 per cent, in valve diseases in 28 per cent, i.e. the number of intercoronary anastomoses increases in myocardial anoxia or hypoxia.

The study of Vastesaeger *et al.* (1957) who used lipoidol for injection into the coronary system is at some variance with the aforesaid works. The authors found anastomoses in 80 per cent of adult hearts, both normal and in various pathological conditions, 7 per cent of the cases being between arteries up to 100 μ in diameter. According to their data, in ischaemic disease the number of anastomoses does not increase. Their markedness is an inborn property and is not dependent on the age or connected with stenosis and occlusion of the coronary arteries. The latter cause only functional hypertrophy of pre-existing anastomoses and collaterals. Ravin and Geever (1946), on the contrary, emphasize the influence of coronary stenotic atherosclerosis on the development of anastomoses, and consider that slowly progressing stenosis fosters their development and may even prevent myocardial infarction in thrombosis.

Pitt (1959) who introduced plastic beads 35-40 and 75-90 μ in diameter into the coronary arteries under the pressure of 100 mm Hg holds the same view. According to his data, in normal hearts, anastomoses occur rarely (one in 15 cases), but are very often found in myocardial infarctions and fibrosis, occlusions of coronary arteries (in 75-100 per cent) and somewhat less frequently in myocardial hypertrophy and heart disease (43-50 per cent). Prinzmetal *et al.* (1948) obtained quite different results in cases of normal hearts: on introduction of glass beads 40-200 μ in diameter under the pressure of 200 mm Hg anastomoses (more than 40 μ in diameter) were

found in most of the normal hearts. Laurie and Woods (1962) employing the gelatin filling method discovered anastomoses in 60 per cent of normal hearts. Spain *et al.* (1963), however, hold that sudden death of young people (35-55 years of age) is caused precisely

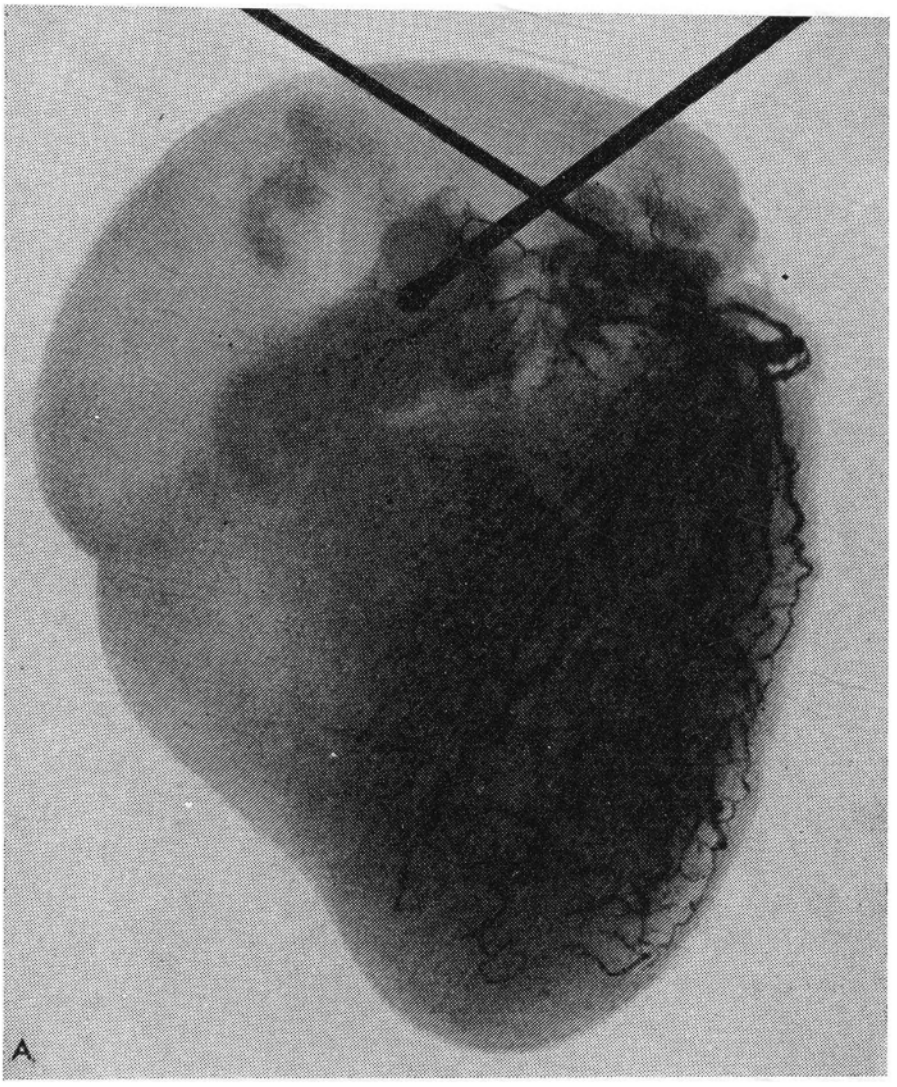

Fig. 8. Absence of anastomoses between the systems of the left and right coronary arteries. A contrast medium administered into the left coronary artery does not penetrate into the system of the right artery (*A*). The reservoir of the latter fills only on subsequent administration of the contrast medium into the right coronary artery (*B*)

by the absence of anastomoses. They found no anastomoses in examining the hearts of the 105 suddenly died.

Anichkov *et al.* (1956) and Smoliyannikov and Naddachina (1963) noted the development of abundant anastomoses in stenotic atherosclerosis. The latter authors emphasize two factors. First, the

number of anastomoses considerably increases only in nonuniform stenotic atherosclerosis when the conditions are created for an irregular decrease in the blood flow through one of the arteries. Second, the frequency of anastomoses considerably varies with the type

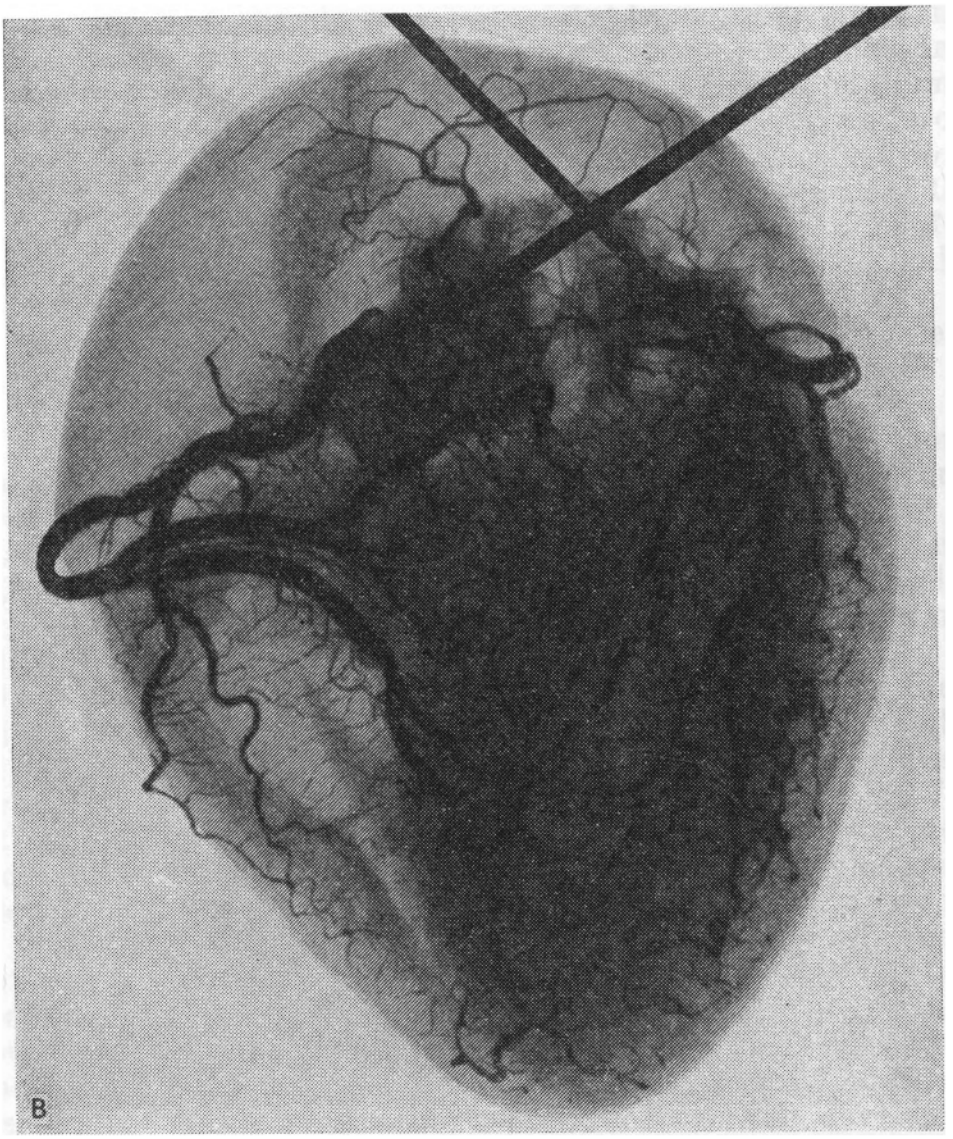

Fig. 8. (continuation)

of blood supply to the heart; in the right and left type they are much fewer than in the median type. On the basis of our own data obtained by method of angiography we can speak of considerable variability of anastomoses[1]. Other conditions being equal (the absence

[1] The vessels were filled with a special mass 'Mixobar' by the method suggested by the cardiovascular department of the WHO under a constant pressure of 160-180 mm Hg and a constant viscosity and size of particles.

or weak manifestation of atherosclerosis or any other signs of coronary insufficiency, and equal weight of the heart) in most cases only the reservoir of the injected artery is filled and there are no signs of anastomoses (Fig. 8). In individual cases, however, the

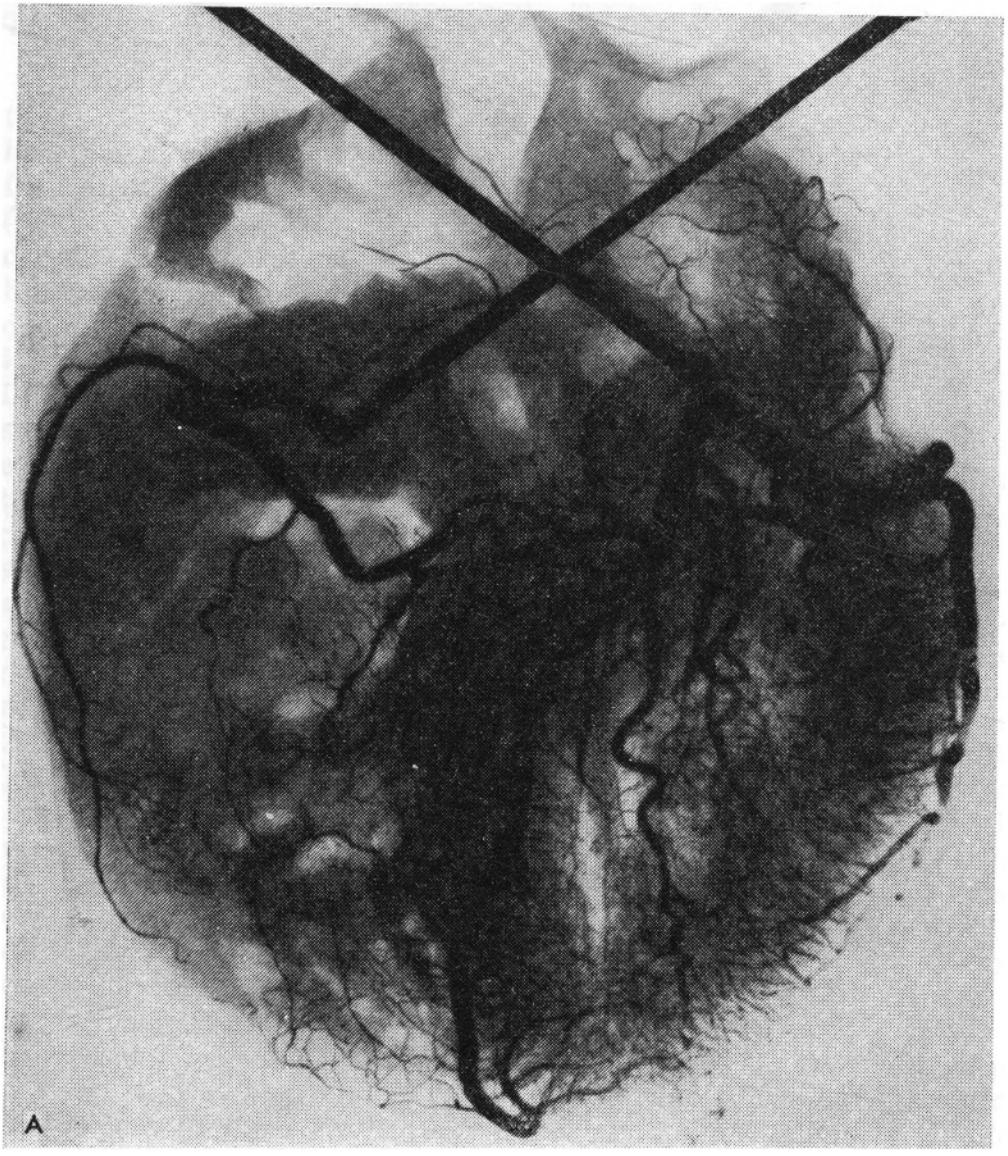

Fig. 9. Filling of the system of the right coronary artery on administration of a contrast medium into the left coronary artery (*A*). Subsequent administration of the contrast medium into the right artery only somewhat increases the filling of small vessels (*B*)

entire coronary system of the heart can be filled through one of the coronary arteries, usually the left and sometimes the right (Fig. 9). In these cases there are no large anastomoses, and the reservoir of the other artery is apparently filled through small branches and

pre-arterioles. Like Smoliyannikov and Naddachina, we gather the impression that a better anastomosis develops (especially in the interventricular septum) in the median type of circulation.

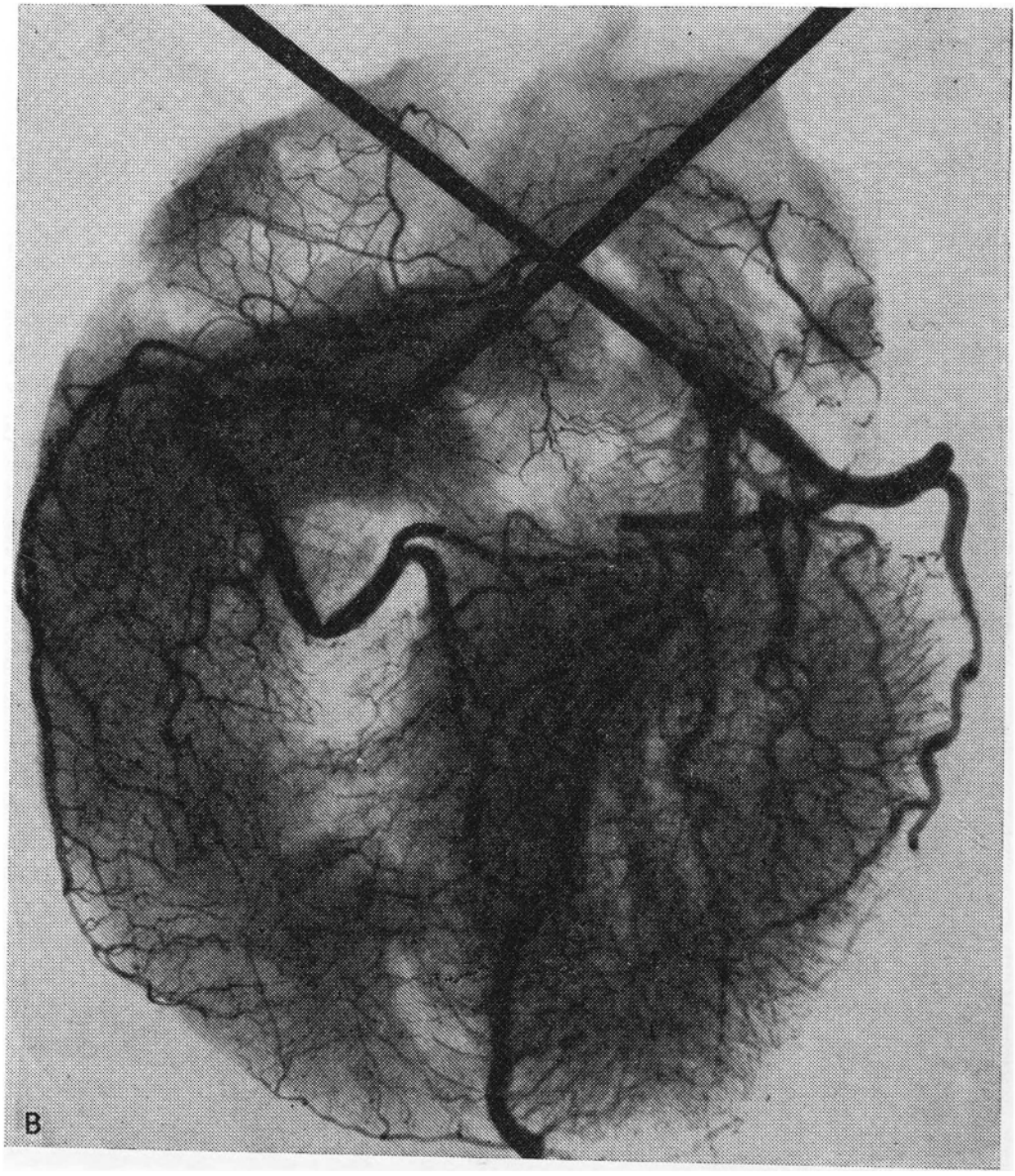

Fig. 9. (continuation)

Thus the literary data and our own observations warrant the assumption that in the normal heart the reservoirs of different arteries communicate mainly through arteries of a small diameter (arterioles and pre-arterioles) and that the available network of anastomoses cannot always ensure the filling of the reservoir of one artery by introduction of a contrast medium into another. In pathological conditions in coronary atherosclerosis, especially in the stenotic

form, or after thrombosis, the network of anastomoses sharply expands and, what is particularly important, their calibre becomes much larger. They are found between branches of the fourth or fifth order.

The Coronary Arteries

In the overwhelming majority of cases of myocardial infarction there are atherosclerotic changes in the coronary arteries of the heart, which increase with age. Studies conducted by the Centre for Studying the Epidemiology and Pathology of Atherosclerosis (Vikhert *et al.*, 1967) show that the area covered by atherosclerotic changes[1] (Fig. 10, *A*) is the largest at any age in the descending branch of the left coronary artery; in the right coronary artery these changes are somewhat less strongly pronounced, but the difference is statistically not always reliable. The circumflex branch is involved in the process the least. It should be remembered that pure lipoidosis takes up in the coronary arteries an area which usually does not exceed 2 or 3 per cent, rarely 5 per cent, of the total area of the intima, and, consequently, it is mainly a question of fibrous plaques, calcinosis and complicated lesions[2]. The same correlations are observed in diabetes[3] and in practically healthy people (both males and females) who died of accidental causes. In hypertensive vascular disease the affected area is somewhat larger in the right coronary artery. But the greatest incidence of stenoses in men and women (stenoses exceeding 50 per cent of the vessel lumen were taken into consideration) is encountered in the anterior descending branch (Fig. 10, *B*). This warrants the assumption that precisely this artery is affected by atherosclerosis the most severely. Occlusive lesions are also most commonly observed in the anterior descending branch. According to Mallory *et al.* (1939), occlusion of this artery was observed in 52 of 70 cases. Jetter and White (1944) cite the following correlations: occlusion of the anterior descending branch was found in 192 fatal cases, of the circumflex artery in 60 and of the right coronary artery in 59 (in most of the cases it was due to thrombosis). Hochrein (1945) cites data from 13 studies: 68 per cent of occlusions were found in the anterior descending artery, 21 per cent in the right artery, 8 per cent simultaneously in both arteries, and 6 per cent in the circumflex branch of the left coronary artery. This circumstance apparently accounts for the fact that infarction most commonly occurs in the region of the anterior wall of the left ventricle, i.e. in the reservoir of the blood supply

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[1] Determined total area of all types of atherosclerotic changes in proportion to the area of the vascular intima.

[2] The latter include haemorrhages into the plaques, their ulceration and thrombosis.

[3] Cases of 'pure' diabetes without hypertensive vascular disease have been studied.

of the anterior descending branch. Indications of the prevalence of this localization of infarction may be found in the studies of Glazova (1949), Dikshtein (1956), Yasakova (1956), Smoliyannikov (1958), etc.

In most of the cases the region of infarction coincides with the reservoir of the affected artery, especially in young people with feebly marked atherosclerosis. But sometimes in stenotic atherosclerosis of one or two coronary arteries or occlusion of one of the bran-

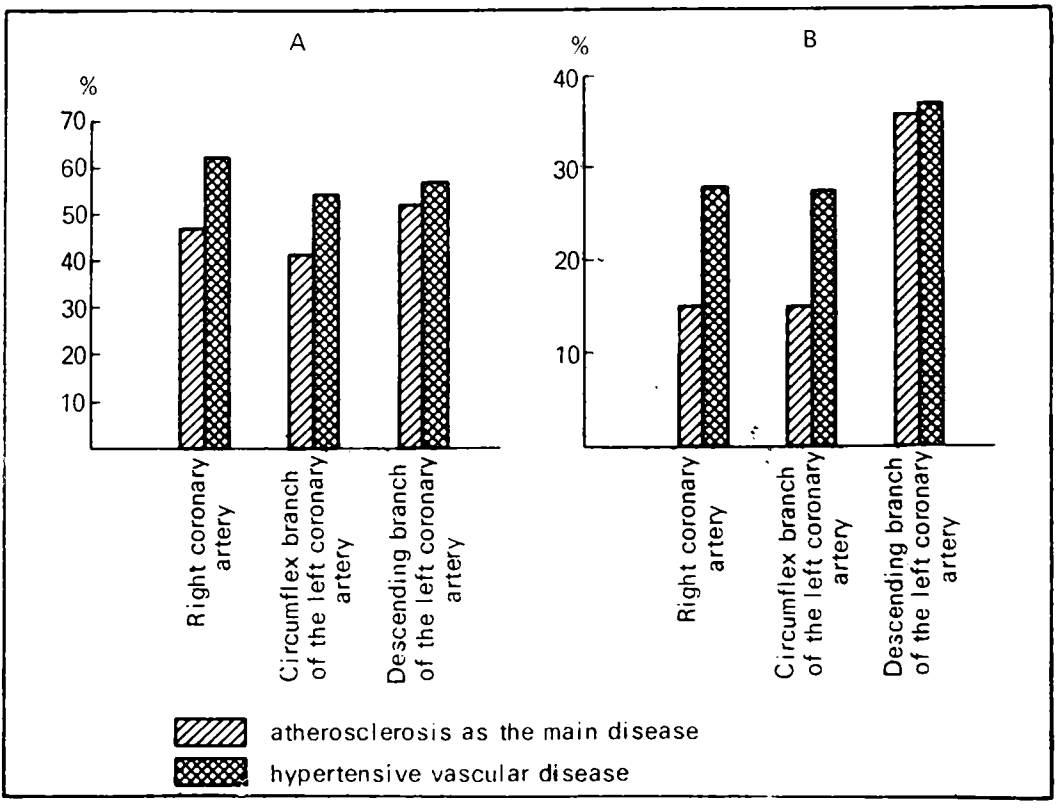

Fig. 10. Atherosclerotic changes in the coronary arteries

ches the reservoir of the thrombosed artery may not coincide with the area of the infarction. In literature on pathological anatomy there is special term 'infarct at a distance' which reflects this phenomenon. This discrepancy is due to the development of collateral circulation and the subsequent catastrophe (e.g. a new thrombosis) in the vessel which supplies the blood to the parts of the myocardium belonging to the reservoir of another artery. For example, slow stenosing in the anterior descending branch creates myocardial ischaemia in the anterior wall of the left ventricle. This serves as a stimulus for the development of collaterals from the left circumflex artery which, as the stenosis in the descending branch progresses, gradually undertakes to supply blood to the ischaemic region. When

the circumflex branch is thrombosed, an 'infarct at a distance' develops in the anterior wall in the region formally belonging to the reservoir of the anterior descending branch. Essentially this happens in connection with the sharp stenosing of the latter and deterioration of the blood flow through it long since proceeding from the circumflex branch and in virtue of the development of collaterals being in the reservoir of its blood supply. In most cases an infarction of the right ventricle actually occurs according to the same pattern (upon exclusion of the collateral blood circulation effected by one of the branches of the left coronary artery in cases of severe stenosing atherosclerosis of the right).

Although in most cases all the manifestations of coronary insufficiency occur with severe atherosclerosis, in a certain percentage of cases of death from myocardial infarction there is a minimum of atherosclerotic changes in the coronary arteries. The number of such observations ranges from several tenths of a per cent to 10 per cent. The latter figure is cited by Smoliyannikov and Apatenko (1956). However, Anichkov *et al.* (1956) found feebly marked atherosclerosis of the coronary arteries in myocardial infarction in 3.7 per cent, Shamesova (1956) in only 1.3 per cent, and Strukov *et al.* (1967) in only 2.0-2.8 per cent of cases. Bean (1937) noted insignificant atherosclerosis in only four patients out of 300 who had died of infarction. Wartman and Hellerstein (1948) did not found either occlusion or atherosclerotic lesions of the vessels in 3.8 per cent of 160 cases. Gross and Sternberg (1939) described 15 fatal cases of myocardial infarction with a minimum of changes in the coronary arteries (a slight thickening of the intima with some narrowing of the lumen) but 13 of them had suffered from hypertensive vascular disease. At postmortem examination of 511 patients with atherosclerosis we observed four cases of myocardial infarction with fatal outcomes and feebly marked atherosclerosis.

Pathological Anatomy

Myocardial infarction is an area of necrosis in the heart muscle caused by cessation of the blood flow or of its flow in amounts in sufficient to cover the functional needs of the moment. Any factor leading to the cessation or a sharp decrease in the coronary blood flow or preventing its increase when the need of the myocardium in oxygen has increased can be the cause of an area of necrosis in the heart muscle. We shall dwell on the pathogenesis of myocardial infarction in greater detail below and now we shall only point out that total cessation of circulation in any of the coronary arteries is most commonly caused by an obstruent thrombus (in 60 per cent of cases), whereas a decrease in the volume of circulation in the reservoir of the coronary arteries is usually due to stenosing atherosclerosis which prevents an adequate increase in the blood flow in cases of increased functional need of the myocardium.

In most cases myocardial infarction occurs in the reservoir of a thrombosed or stenosed artery. When examined with the naked eye the area of necrosis clearly manifests itself only 18-24 hours after the onset of the disease which is indicated in typical cases by the appearance of retrosternal anginose pains often with a characteristic radiation (see Chapter 4). If the patient dies a few hours after the development of clinical symptoms the area of necrosis is not clearly seen. In the area supplied with blood by the affected artery the myocardium is somewhat flabby and not uniformly filled

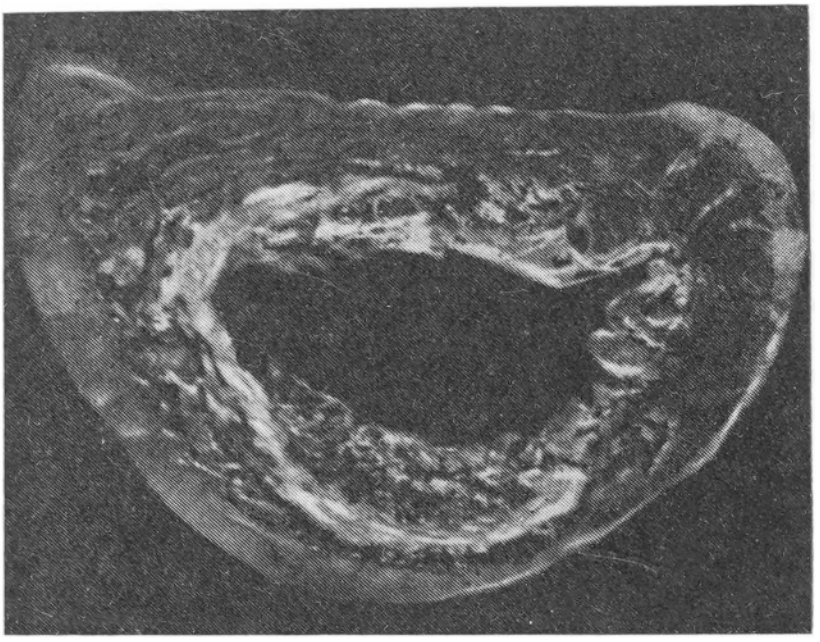

Fig. 11. Extensive myocardial infarction spreading to the anterior wall of the left ventricle and the interventricular septum. The zone of infarction shown in the figure is white and well demarcated from the surrounding myocardium

with blood. At the end of the first 24 hours the area of necrosis can be clearly seen as a portion (or portions) of irregular outlines, clayey or clayey-reddish colour often surrounded by a red strip of haemorrhage and, as a result of oedema, somewhat bulging above the surface of the incision. Owing to the serous oedema and phenomena of autolysis the area of infarction differs from the surrounding tissues by its flabbiness (myomalacia). As the oedema subsides the infarction area sinks, its surface becomes dryish, its consistency dense and its colour yellowish-gray or yellowish-green with the result that this area clearly stands out against the background of the surrounding myocardium (Fig. 11). It is surrounded by a narrow reddish border which is a young, rich in dilated thin-walled vessels connective tissue, which gradually expands to the centre of the affected area and replaces the necrosed muscle fibres. In three to five

weeks (depending mainly on the size of the initial area of necrosis) in its place first arises a connective-tissue scar reddish-gray in colour which is composed of young granulation tissue abounding in blood vessels. As it matures in uncomplicated cases its area somewhat decreases and its colour grows grayish-white. A whitish dense scar forms in the end and replaces the muscular tissue (Fig. 12).

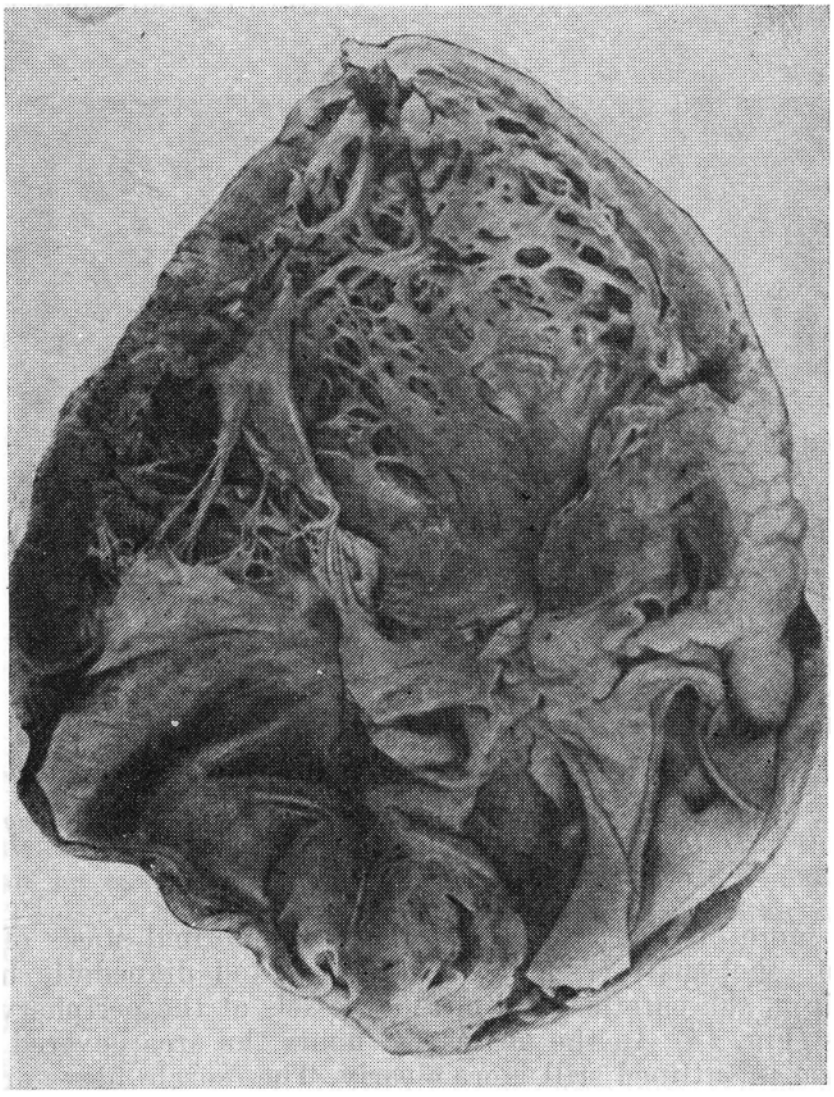

Fig. 12. Postinfarction scar covering the entire apex. The wall of the left ventricle is sharply thinned out

Healing of myocardial infarction was first described in 1880 by Weigert who noted that it followed the course like that of any infarction in the body, i.e. by elimination of the necrotic masses and their replacement first by granulation tissue and then by scar tissue. Weigert also noted such complications of infarction as pericar-

ditis and parietal thrombosis, and also the processes of their organization.

Examination under a usual light microscope shows the first changes in the infarction area six to eight hours after the onset of the disease. They are displayed by a paralytic dilatation of the capillaries with erythrocyte stases in them, oedema of interstitial tissue, and a certain swelling of the muscle fibres, although the latter retain the transverse striation (Fig. 13). In 10 to 12 hours these changes

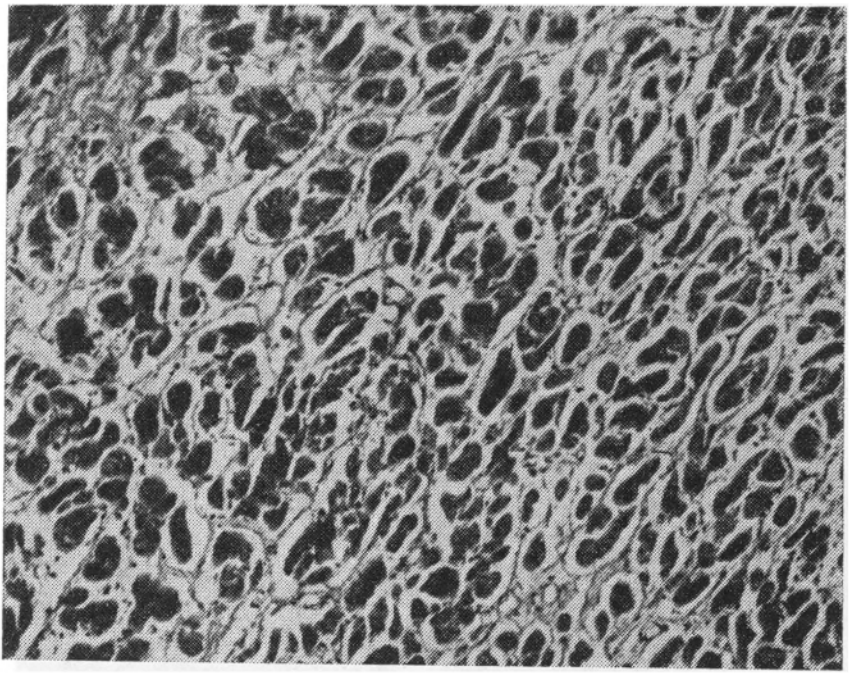

Fig. 13. Sharp oedema of the myocardial interstice in the region of a fresh infarction. Death ensued seven hours after the beginning of the pain syndrome. Stained with haematoxylin-eosin. Magn. x100

become more distinct, they are joined by marginal stasis of leucocytes in the small vessels and sinusoids and diapedetic haemorrhages from the paretically dilatated vessels at the periphery of the necrosis (Fig. 14). In the nearest 24 hours the area covered by the infarction is outlined still more clearly. The muscle fibres are swollen, their outlines become irregular, as if corroded, and their transverse striation is blurred and gradually disappears. The sarcoplasm becomes lumpy (Fig. 15), eosinophilic or fuchsinophilic with vacuoles and clearings (Fig. 16). The nuclei become distended and assume the shape of vesicles (Fig. 17) or, on the contrary, become pyknotic, dense and structureless (Fig. 18). The interstices accumulate basophilic amorphous or delicately fibrous substance which yields β- and γ-metachromasia when stained with toluidine blue; they also accumulate PAS-positive substances. The walls of small

arteries in the area of an extensive infarction also become swollen, their pattern becomes blurred, and the lumen is filled with a homogenized mass of erythrocytes. At the periphery of the lesion a process of mass egression of segmented cells begins from the intact vessels, forming at the border with necrotic tissue first loose (Fig. 19) and then compact accumulations which mark the zone of demarcation.

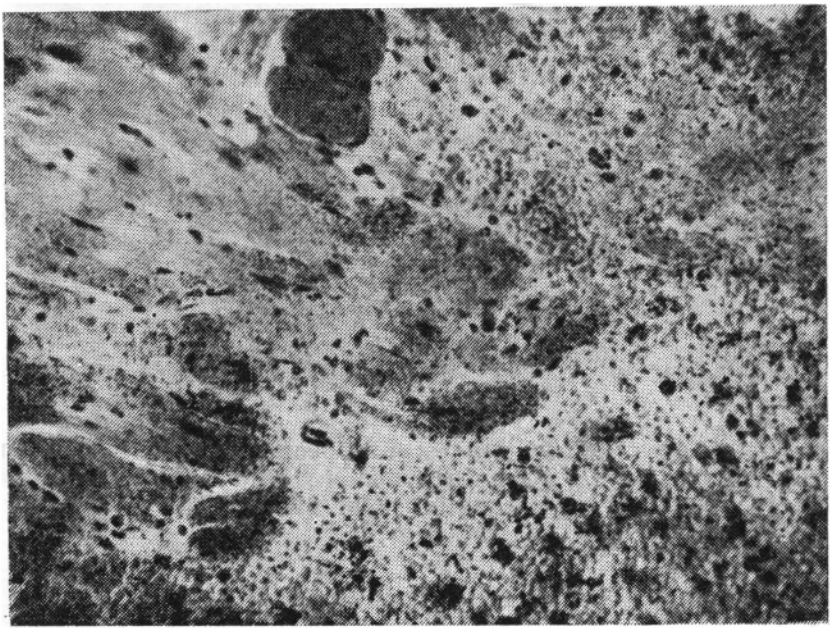

Fig. 14. Vast haemorrhage on the verge of infarction. Intact muscle fibres seen on the left. Stained with haematoxylin-eosin. Magn. x250

Its development reaches the maximum between the second and fourth days after the onset of the infarction (Fig. 20).

By means of an electron microscope the changes in the infarction area can be revealed already in 30 minutes (Strukov and Mitin, 1967). They consist in deformation of mitochondria, their swelling, and vacuolization and partial destruction of the cristae. The authors regard these changes as possibly reversible. This coincides with the experimental findings of Vinogradov (1957) who applied a temporary ligature to the anterior descending artery of the rabbit's heart and upon removing it within 10 to 15 minutes observed no development of infarction. Early changes are accompanied by a loss of glycogen (it may be a case not of its loss, but its expenditure under conditions of anaerobic existence) and release of potassium ions (Jennings *et al.*, 1960; Raiskina, 1967; Pozdyunina, 1967). A loss of potassium is generally characteristic of injured muscle fibres of the heart (Raab, 1966, and Pozdyunina, 1967). After three to five hours the mitochondria of myofibrils decompose, the number of lysosomes increases, the activity of certain enzymes (ATPase,

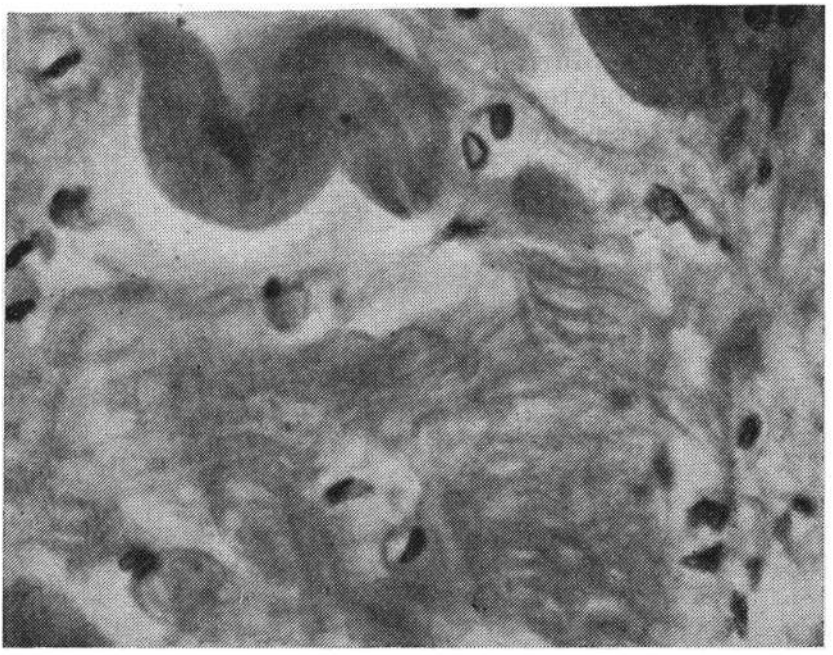

Fig. 15. Early changes in muscle fibres: disappearance of cross-striation, pitted contours of the muscle fibre, lysis of the nuclei. 15-hour-old infarction. Stained with haematoxylin-eosin. Magn. x650

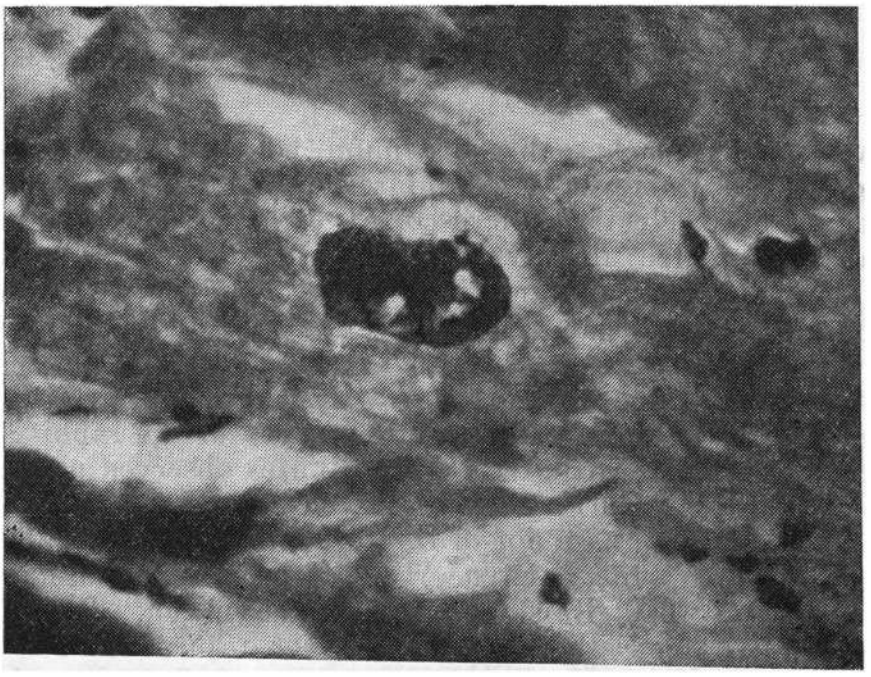

Fig. 16. Vacuolization of the cytoplasm and nucleus of the muscle fibre in the infarction zone. 18-hour-old infarction. Stained with haematoxylin-eosin. Magn. x650

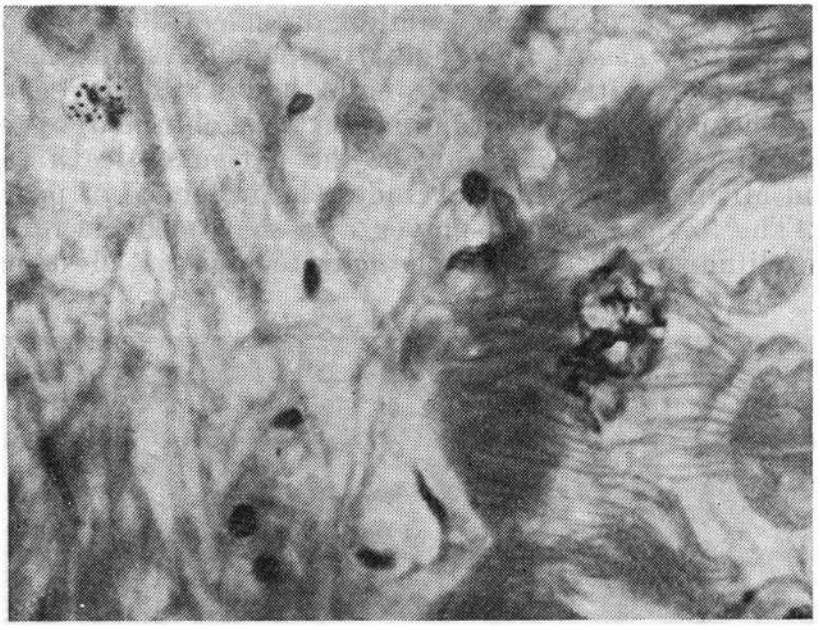

Fig. 17. Vacuolization and partial lysis of the nucleus of the muscle fibre Cross-striation still discernible. 12-hour-old infarction. Stained with haema toxylin-eosin. Magn. x650

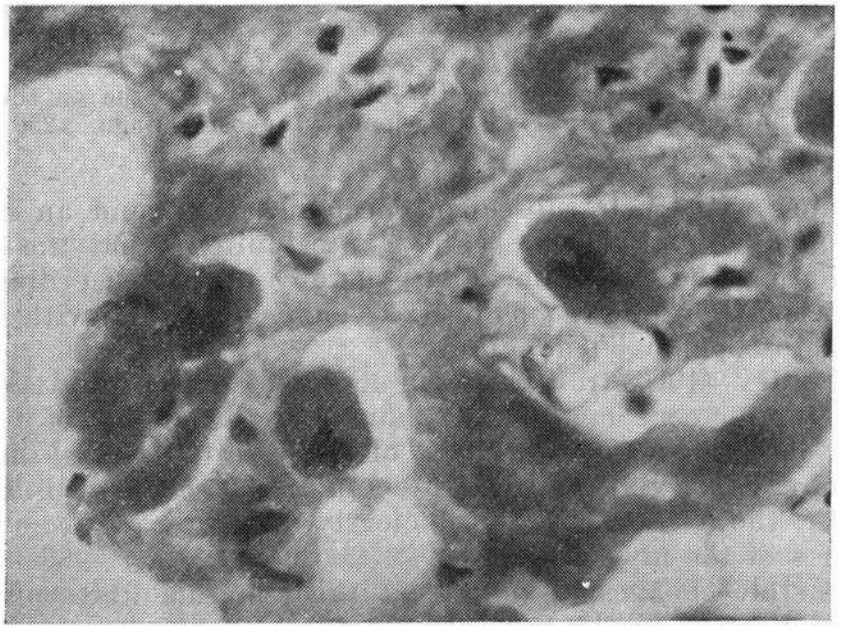

Fig. 18. Lumpy disintegration of the sarcoplasm, pyknosis of the nuclei of muscle fibres in the region of infarction. 24-hour-old infarction. Stained with haematoxylin-eosin. Magn. x650

succinic dehydrogenase, nicotinamide dinucleotide-diaphorase) diminishes (Strukov *et al.*, 1967, and Mitin, 1969). Analogous changes are found in man within three to eight hours after myocardial infarction. The material for examination was obtained by a transcutaneous biopsy immediately after the patients' death (Strukov, 1958, and Mitin 1969), which excludes the influence of postmortem changes. The changes were displayed in a sharp oedema of the stroma, a swelling and vacuolization of mitochondria, destruction of

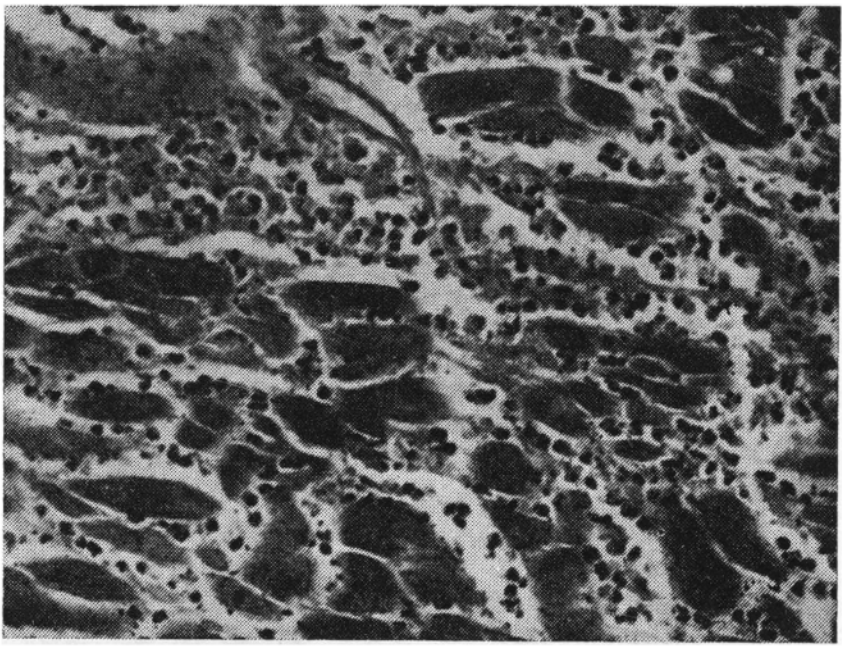

Fig. 19. Emergence of segmented cells into interstitial tissue on the border of infarction. Stained with haematoxylin-eosin. Magn. x250

membranes with their subsequent decomposition, and an increase in the number of lysosomes (Fig. 21). It follows that the area of infarction can be determined (and thereby its presence diagnosed) with a usual light microscope in six to eight hours, and with an electron microscope in 30-45 minutes.

Kondratiev (1966) revealed the area of myocardial ischaemia by the luminescent method. A change in the colour of luminescence of the injured myocardium is observed in the area of disturbed blood circulation three hours after the occurrence of ischaemia. Moreover, the ischaemic lesion is clearly distinguished from the intact parts of the myocardium.

Irreversible changes in the structure of muscle fibres and their destruction occur in the myocardium three to five hours after cessation of circulation. This is followed by processes aimed at removing the necrotic parts, on the one hand, and at replacing them by connective tissue, on the other. As is known, myocardial fibres

are incapable of complete regeneration with replacement of the destroyed contractile elements by other, functionally adequate. Necrosis of myocardial fibres in man, as well as that produced experimentally in animals, is, regardless of its cause, followed by the formation of a connective-tissue scar (Gornak, 1960; Bing, 1961, and Strukov *et al.*, 1967).

The participation of muscle fibres in forming young granulation tissue is not excluded, which permitted Oppel to speak of 'myogenic

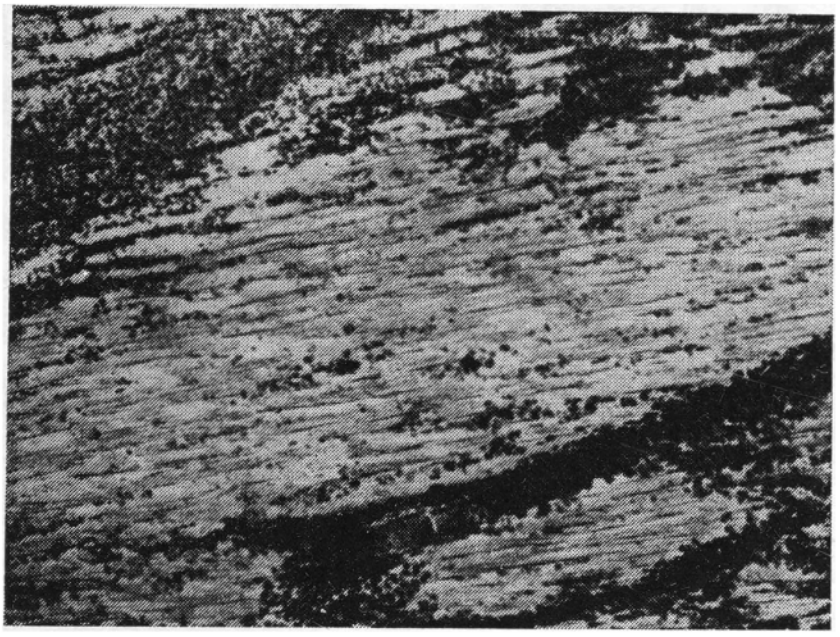

Fig. 20. Demarcation leucocyte zone of the border of infarction. Stained after Goldman. Magn. x100

granulation tissue' as far back as 1901. This was subsequently confirmed by Lavrov (1949); Kashaev (1951), and Skuba (1968). The participation of muscular elements in forming the connective-tissue scar was also mentioned by Rumyantsev (1953); Sinitsyn (1959), and Polezhaev *et al.* (1961). But these cells of muscular origin are, as Oppel puts it, 'sick cells'. As the studies of Lavrov (1949); Kashaev (1951), and Skuba (1968) show, they are not subject to further differentiation and soon destroyed. There are some works, however, which convincingly show the possibility of regeneration of the heart muscle elements with formation of functionally adequate fibres in newborn animals (Rumyantsev, 1953, and Robledo, 1956). But myocardial infarction is mainly the lot of the middle-aged and elderly people, and the sings of regeneration of muscular elements that may be discovered in studying the processes of healing in man (formation of giant cells with oval or spindle-shaped nuclei, whose

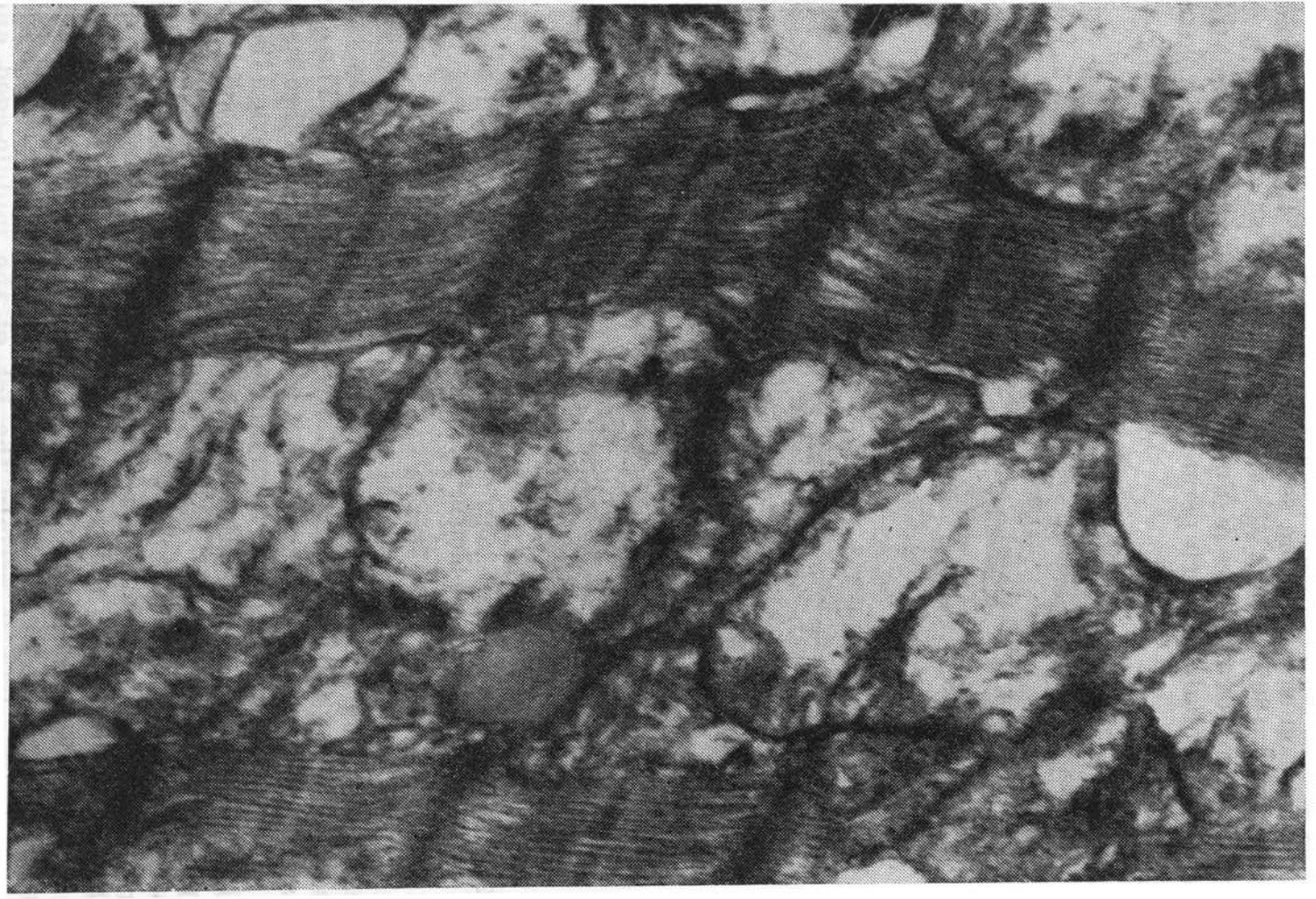

Fig. 21. Changes in the mitochondria in the zone of 3-hour-old experimental infarction. Magn. x9600

muscular origin is indicated by clear transverse striation in the cytoplasm) are of no practical importance.

There is a good deal of literature on various aspects of the healing of myocardial infarction, both in experiment and in man. One of the first experimental studies was that of Baumgarten in 1899. Karner and Dwyer (1916) who ligated the left coronary artery in dogs gave a detailed description of this process. During the last decades this problem has also attracted the attention of Soviet and foreign researchers, which has been reflected in numerous publications. The course of experimental myocardial infarction has been described, in particular, by Shakhbazyan (1940); Smoliyannikov and Apatenko (1956); Vinogradov (1956); Gornak (1960); Gornak and Lushnikov (1963); Strukov *et al.* (1967) and also by a number of foreign authors (Baumgarten, 1899; Karner and Dwyer, 1916; Kent and Diseker, 1955; Jennings *et al.*, 1960; Klionsky, 1960; Shnitka and Nachlas, 1963).

In general the healing of myocardial infarction in man has been described by Mallory *et al.* (1939); Abrikosov (1947); McDonald and Bentley (1951); Shamesova (1956); Barrie and Urbach (1957); Kalitievskaya (1957); Smoliyannikov and Naddachina (1963); Davydovsky (1965); Strukov *et al.* (1967), and many others.

It is not our purpose to give a detailed analysis of all these studies. It was very well done in the monograph of Strukov *et al.* (1967). We shall only mention that, according to Strukov's correct statement, the morphogenesis of myocardial infarction is very similar in experiment and in man, whereas the pathogenesis differs entirely, i.e. a mere ligature of the coronary artery in an experimental animal in no way reflects the complexity of the pathogenic mechanisms of disturbances in the coronary circulation of man. In experiments myocardial infarction heals faster than in man. This is quite clear if we consider that, first, the reparative potentialities of connective tissue are much higher in animals than in man; second, the experiments are mainly carried out on young animals; and, third, under experimental conditions the infarction heals in the absence of stable disorders of coronary circulation, which always take place in man owing to the presence of stenosing atherosclerosis of the coronary arteries.

Of some interest are the works in which the healing of infarction is considered from the standpoint of time that has elapsed since the moment of its onset. On the one hand, this gives a correct idea of the character of the process at each particular moment of the disease and in some measure predetermines the medical tactics of caring for the patients and, on the other hand, makes it possible to understand the causes and genesis of the developing, or capable of developing, complications of the infarction, and, to a certain extent, to prevent them. Such a clear temporal exposition of the events is given in the studies of Mallory *et al.* (1939); Lodge-Patch (1951), and in the latest monograph of Strukov, Lushnikov and Gornak

(1967). The works described above contain similar information, but since Lodge-Patch's study offers a very convenient diagram of the reparation processes (Fig. 22) we shall adhere to it in our further exposition.

The earliest changes recorded six hours after the onset of infarction consist in oedema of the interstices, paretic polyaemia of the capillaries and small haemorrhages at the periphery (see Figs. 13

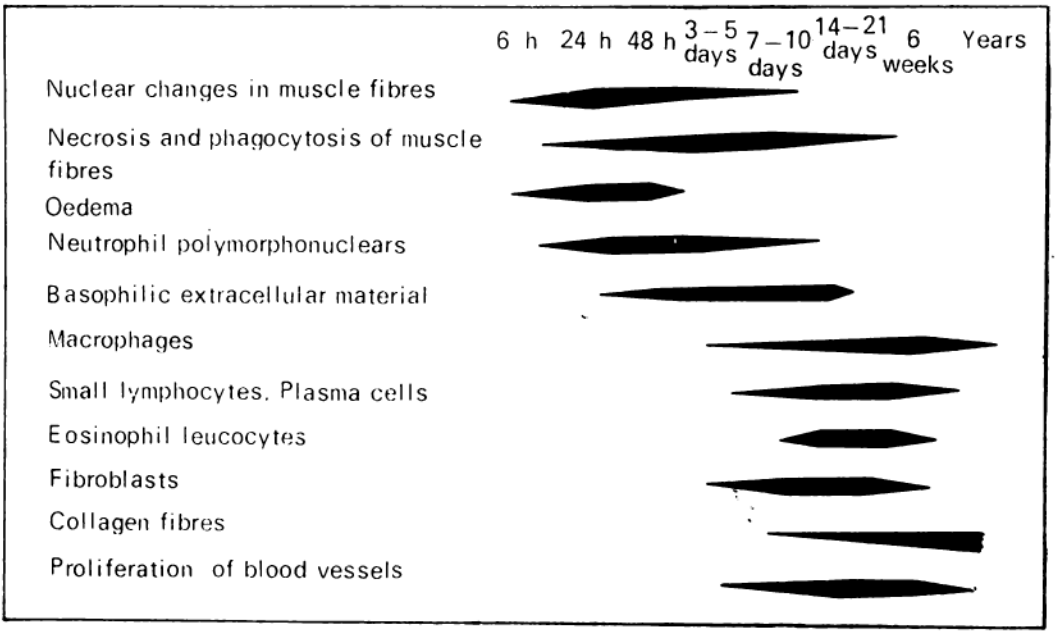

Fig. 22. The character of the cellular exudate at various stages after cardiac infarction (after Lodge-Patch)

and 14). In the muscle fibres there are either minimal changes or no changes at all. Subsequently the oedema increases and persists for one and a half to two days, gradually diminishing. In twelve hours signs of destruction of muscle fibres are revealed microscopically: swelling, blurring of transverse striation, eosinophilia or fuchsinophilia (see Figs. 15-17), and nuclear pyknosis. They are most clearly manifest in 24 to 28 hours (homogenization of muscle fibres, their 'transparent' glassy appearance, break up of the sarcoplasm into separate lumps, appearance of drops of neutral lipids, especially at the periphery of the infarction) (Figs. 18 and 23). Subsequently decomposition of the necrotized fibres and their resorption begins (which corresponds to the term 'myomalacia').

The greater part of muscle fibres, stroma and vessels are usually destroyed in the infarction area. True, by examining the subsequently developing scars it is possible to find in them single hypertrophied muscle fibres surrounded by a scar tissue. This indicates that for some reason or other single fibres are, nevertheless, preserved. Sometimes one may see along the vessels of Vieussens and The-

besius a narrow (2-3 mm) strip of intact muscle fibres, and also small isles of muscle fibres and stroma near single vessels (Fig. 24). Subsequently these isles of connective tissue play a certain role in replacing the infarction area by connective tissue, thereby constituting peculiar points of growth. In extensive infarctions, however, all tissue elements undergo necrosis.

Single neutrophil leucocytes can be seen in the oedematous fluid as soon as six hours after the onset of infarction. Later their number rapidly increases. In 48 hours they form copious accumulations at the periphery of the infarction between the dead and intact muscle

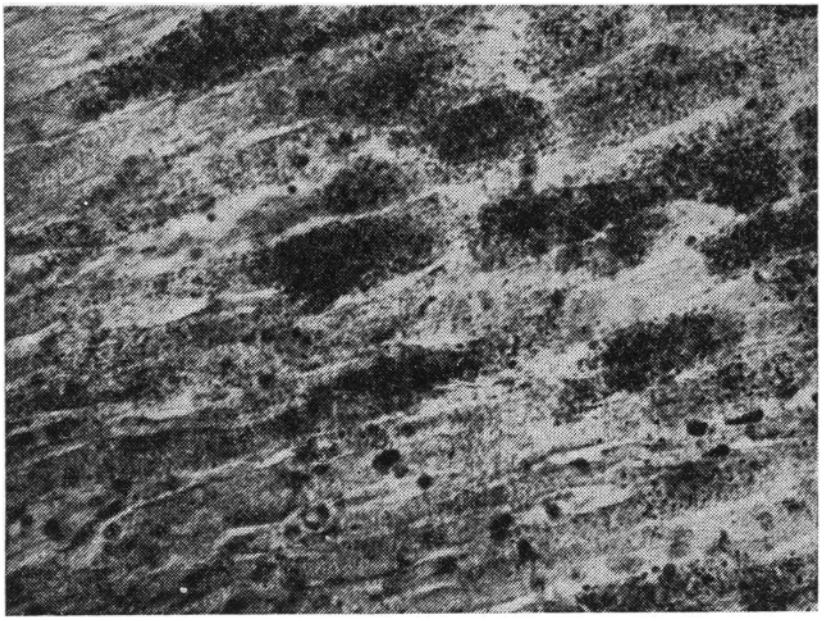

Fig. 23. Small-drop adiposis of the intact muscle fibres on the border of 36-hour-old infarction. Stained with oil red. Magn. x250

fibres (see Fig. 19). The neutrophil leucocytes prevail until the third or fifth day, but the process of their destruction and decomposition begins on the third day; at first it is feebly marked, but later it assumes a mass character so that the entire line of demarcation is an area of dying neutrophils and their nuclear detritus (Figs. 20 and 25). The neutrophil leucocytes do not participate in the phagocytosis of the dead muscle fibres, but apparently secrete proteolytic enzymes which are conducive to their lysis. Toward the end of the 10th to 12th day all traces of the leucocyte reaction usually disappear.

Lastly, basophilia of the stroma and accumulation in it of acid mucopolysaccharides which yield a metachromatic reaction when stained with toluidine blue are also characteristic signs of the early period of myocardial infarction. Argyrophilic fibres of the stroma

swell and decompose. Strukov associates the appearance of metachromasia with changes in the ground substrate of connective tissue in the infarction area to a lesser extent of the fibrous structures. It is not excluded that they are due to the accumulation of hydrogen ions and a shift of the pH of the medium in the acid direction.

On the basis of histochemical studies of redox enzymes in the area of experimental infarction during early periods (from 12 hours to four days). Lushnikov (1962) suggests distinguishing three zones:

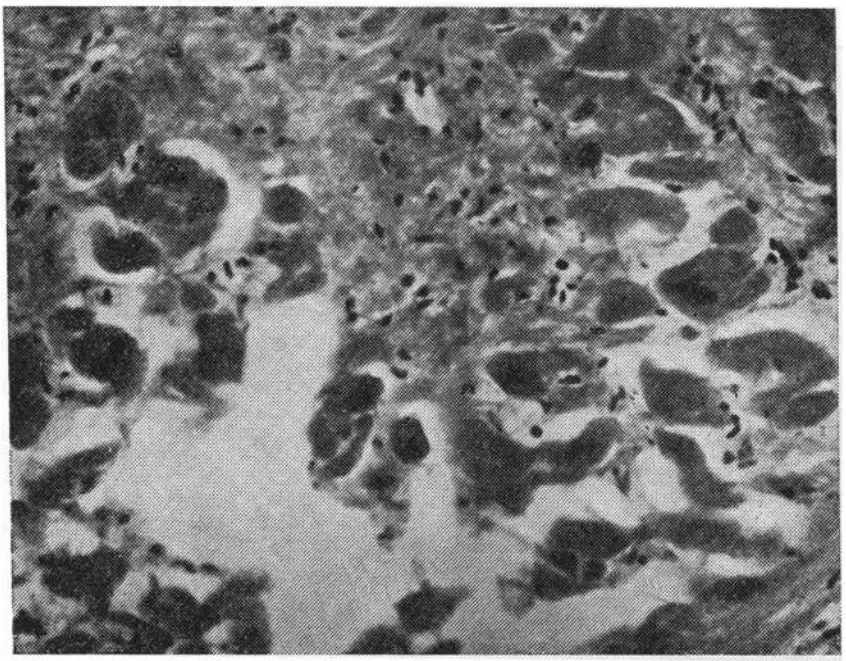

Fig. 24. Separate muscle fibres preserved near the vessels in the zone of infarction. Stained with haematoxylin-eosin. Magn. x250

(1) total depression of enzymatic activity and, consequently, destruction of the muscle fibres; (2) diminished activity when the changes under favourable conditions are still reversible; (3) retained or even increased activity of the redox enzymes. The fate of the middle zone, i.e. its result in necrosis or the reversibility of the changes apparently depends on the state of collateral circulation and the level of cardiac activity. In the already formed infarction (after four days) there are only two zones—the first and third.

Resorption and phagocytosis of necrotized muscle fibres are effected by the macrophagal cells which appear on the fourth day at the periphery of the infarction on the outside of the leucocytic ridge (Fig. 26). Subsequently their number increases, reaching the maximum by the sixth week. They may persist in small numbers for up to two years. Their main function is to clear the area of the destruction of muscular tissue and to absorb decomposition products.

Fragments of muscle fibres, pigment and fat droplets can be seen in their cytoplasm. In the macrophages fat is usually discovered on the ninth day.

Lymphoid cells appear along the edge of the infarction on about the fourth or fifth day, and plasma cells—on the seventh or eighth day, at first few and then in larger numbers, reaching the maximum toward the end of the third week. Their appearance is apparently connected with the immunological changes which occur at about

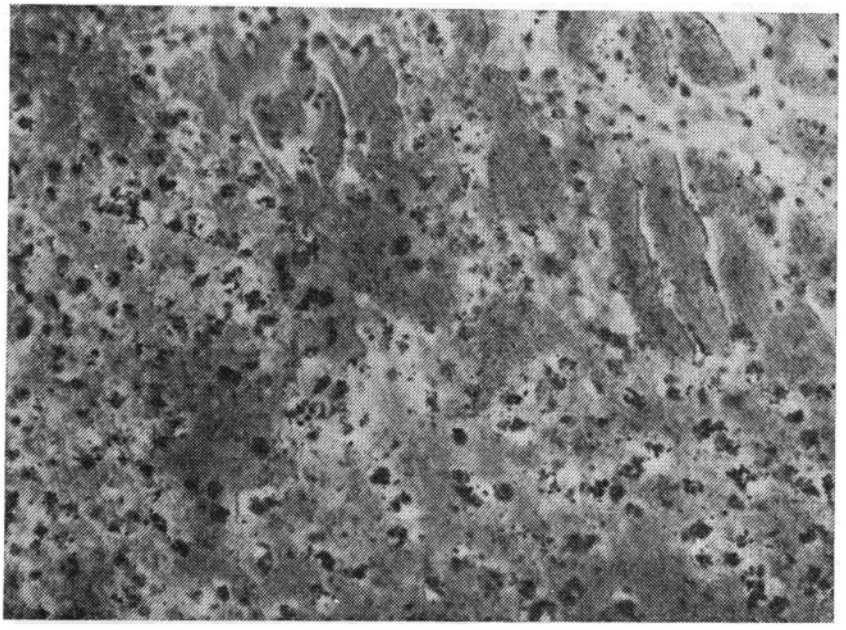

Fig. 25. Mass disintegration of leucocytes in the demarcation zone of a 4-day-old infarction. Stained with haematoxylin-eosin. Magn. x250

the same time and to which considerable importance in the development of auto-allergic processes in myocardial infarction is now attached. The plasma cells and lymphocytes may persist in the infarction area for many months.

The appearance of eosinophilic leucocytes is a less constant sign. They can usually be seen from the eighth or ninth day to the third or fourth week. Their maximum accumulation is observed between the 12th and 15th days. The fibroblastic reaction occurs on the fourth or fifth day. The first fibroblasts appear at the periphery of the infarction from the isles of the stroma persisting around the vessels, but the development of granulation tissue reaches its height mainly after 10-25 days of the existence of the infarction (Fig. 27). The first thin argyrophilic and collagenous fibres appear on the seventh or eighth day.

Thus during the first and, to a somewhat lesser extent, the second week (since granulation tissue develops rapidly) the infarction area

is a dead field deprived of vessels, steeped in oedematous fluid, pierced by decomposing leucocytes at the periphery and filled with dead lysing muscle fibres. This state is the cause of the earliest and at the same time most dangerous complications of infarction: acute cardiac aneurysm which may lead to relative mitral insufficiency, cardiorrhexis which occurs mainly during the first or second week of the disease, avulsion of the papillary muscles or perforation of the interventricular septum. We shall deal with the conditions conducive to these complications below.

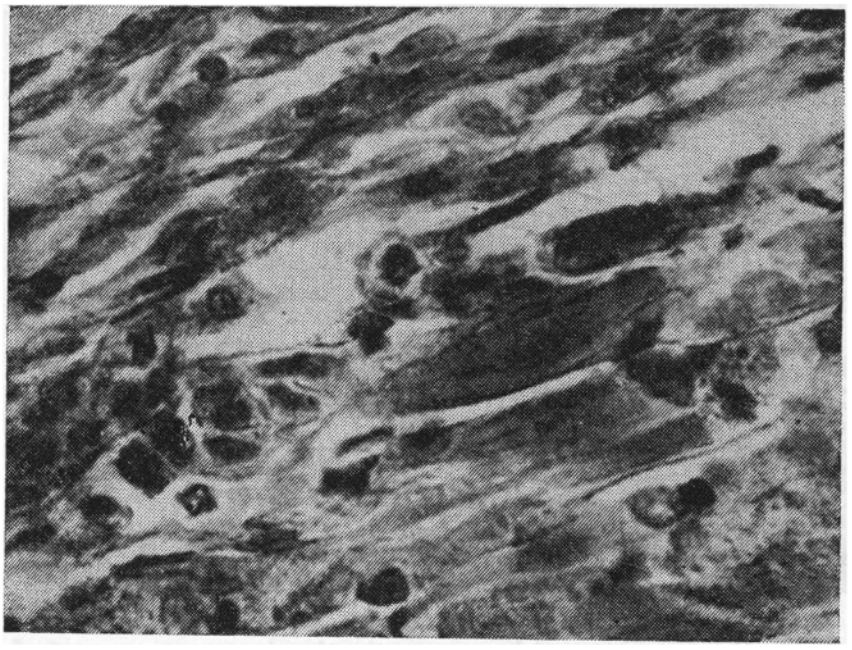

Fig. 26. Macrophages resorbing dead muscle fibres along the periphery of a 6-day-old infarction. Stained with haematoxylin-eosin. Magn. x650

After seven to ten days the reparation processes result in replacement of necrosis by young granulation tissue which proliferates from the surrounding myocardium and the perivascular isles persisting in the depth of the infarction. The vessels begin to grow into the infarction area somewhat later than the fibroblasts start proliferating, namely, on the sixth or seventh day, but by the tenth day the periphery of the infarction turns into a strip of granulation tissue rich in vessels and cellular elements. Owing to the abundance of vessels the strip of young connective tissue looks red in section. During this period the fibroblasts are large and rich in sharply basophilic cytoplasm. Orientation of their longitudinal axis is not outlined yet, and they are arranged irregularly. Staining of the interstitial substance and the few fibrils with toluidine blue reveals a strongly pronounced metachromatic reaction, as is usually the case in any young granulation tissue. At this time (the third week) the

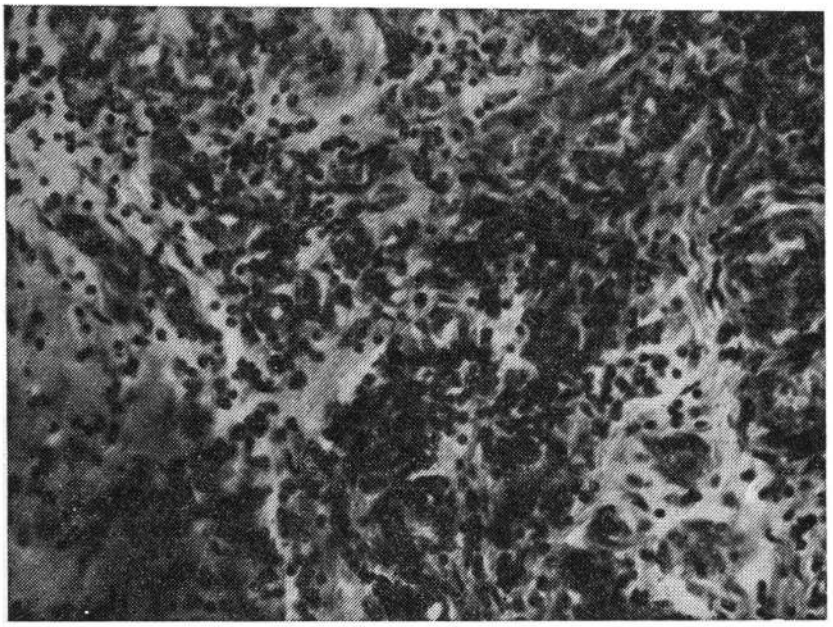

Fig. 27. Young connective tissue with a large number of lymphoid cells along the periphery of a 12-day-old infarction. Stained with haematoxylin-eosin. Magn. x250

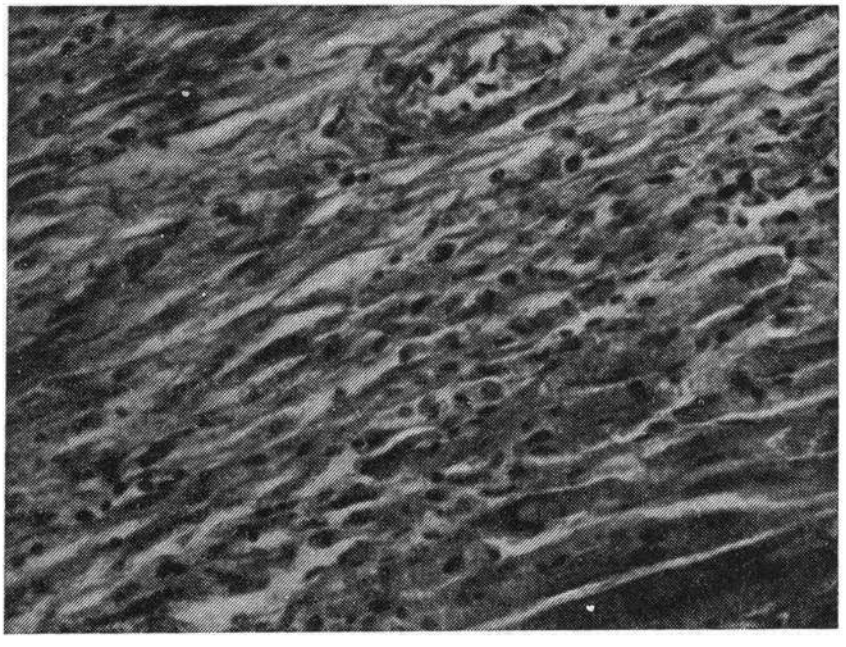

Fig. 28. Connective tissue along the periphery of a 22-day-old infarction is assuming an orderly, unidirectional arrangement. Stained with haematoxylin-eosin. Magn. x250

infarction area seems to shrink and sinks over the surface of the incision. It is gradually completely replaced by connective tissue of various degrees of maturity. It is younger in the central parts and more mature, with features of fibrous tissue, at the periphery. The forming collagenous fibres assume regular arrangement parallel to the free endocardial surface. As the number of fibrous elements increases, fibroblasts shrink in size, their nuclei elongate, the cytoplasm gradually loses its basophilia and becomes less abundant. On the whole the fibroblasts and collagenous fibres assume an or-

Fig. 29. Sinusoids in the postinfarction scar. Stained with haematoxylin-eosin. Magn. x250

derly arrangement oriented parallel to the surface of the endocardium and pericardium, which is observed from the second or third week of healing and persists subsequently (Fig. 28). The infarction is replaced by the granulation tissue at different periods, depending on the initial amount of destroyed muscular tissue, the patient's age and his general condition, and also on the extent of the coronary sclerosis, etc. for which reason it is impossible to indicate the exact time when the process will terminate. It may be considered, however, that in most cases the infarction area is fully replaced by the granulation tissue of various degrees of maturity by the fifth or sixth week. Subsequently only the usual maturation of the latter takes place. The number of cellular elements progressively decreases, but that of collagenous fibres simultaneously increases, they become thicker and coarser; the initial pinkish hues, when stained after Van Gieson, and bluish, when stained after Masson, being replaced by the red or dark-blue. In the end collagenous

fibres completely fill the defects, and a fibrous scar is formed at the site of the former infarction. The initially numerous capillaries and thin-walled vessels become obliterated, their number sharply decreases, and in the scar they are mostly represented by sinusoids with weakly developed elements of vascular wall (Fig. 29). Obturator-type vessels or arteriovenous anastomoses shunting the scar area can be seen at the periphery. Here and there there are isles of hypertrophied or, on the contrary, atrophic muscle fibres with dystrophic changes. The fibrous scar is fully formed by the third or fourth month, but its further evolution, its maturation may take a much longer time (Mallory *et al.*, 1939; Lodge-Patch, 1951; Kalitievskaya, 1957; Gornak, 1960; Strukov *et al.*, 1967, etc.).

Subendocardial Infarction or Myocardial Necrosis

Subendocardial infarction has long been distinguished by some authors (Büchner, 1939; Friedberg and Horn, 1939, and Master *et al.*, 1941) as a peculiar form of the disturbance of coronary circulation usually associated not with occlusion or thrombosis of the coronary arteries, but merely with their severe atherosclerosis. Horn *et al.* (1950) regard subendocardial infarction as a manifestation of protracted coronary insufficiency that developed in connection with some general aggravating disturbances. They point out that the ECG changes are of a sufficiently definite character: depression of the *RST* segment, negative *T* wave and the absence of *Q* wave (i.e. the changes are directly opposite to those observed in thrombosis of the coronary arteries—elevation of *RST* and the appearance of *Q* wave) which warrant the suspicion of subendocardial necrosis. Of the 25 cases observed in none of them did they found at the autopsy thrombosis of the coronary arteries, but 14 cases exhibited severe, five moderate, and six feebly marked atherosclerosis of the coronary arteries. In most cases (20) the anterior or posterior papillary muscle of the left ventricle, the posterior (17) or anterior (16) wall of the left ventricle, and not infrequently the left-ventricular part of the interventricular septum (15) are affected, whereas the right ventricle is seldom involved in the process (4). Many patients have aggravating factors conducive to the development of necroses. In particular, Horn *et al.* (1950) observed acute heart failure (in five patients), paroxysmal tachycardia (in five), gastro-intestinal haemorrhage (in four), pulmonary embolism (in four), dissecting aneurysm of the aorta (in two), postoperative shock (in one), and severe infection (in one patient), i.e. the conditions accompanied by a fall of the blood pressure and a decrease in the coronary blood flow. These aggravating factors were absent only in four patients. The authors suggest two reasons for the development of necroses precisely in the subendocardial region: first, these parts of the myocardium are located in the most distant parts of the coronary blood

flow and in weakening of the blood flow they turn out to be in the least advantageous position; second, the subendocardial parts of the myocardium are more subject to compression during systole. According to Johnson and Di Palma (1939), the pressure gradient during systole diminishes from the internal (subendocardial) to the external layers; this conduces to the compression of the subendocardial vascular network. Thus the combination of two local factors (remote position of subendocardial layers in the system of coronary blood supply and the high pressure exerted on them during systole) with the general circulatory disorders which usually take place leads to anoxia and the development of necroses embracing circularly the circumference of the left ventricular cavity and often merging in vast fields in this area of the myocardium.

Descriptions of individual cases of subendocardial necroses can be found in the works of Levine and Ford (1950), and Di Cantogno *et al.* (1959). The latter authors use the term 'anoxic necroses'.

Complications

Ruptures of the Heart

Rupture of the heart, as was already stated, is a complication of the early period of myocardial infarction and in the overwhelming majority of cases is fatal. Depending on the topography the following ruptures may be distinguished: external, with the development of haemopericardium and death in a few minutes due to a tamponade in the pericardial sac; and internal, pertaining to the interventricular septum or the papillary muscles with the development of clinical symptoms of acute heart failure.

Rupture of the heart has been known for a long time. By 1925 Krumbhaar and Crowell collected in the literature 654 cases and cited their own 22 observations. Three years later Davenport described 35 cases, in 1929 Levine and Brown described nine cases, and in 1930 Beresford and Earl another 46 cases. Mention may be made of the studies of Mallory *et al.* (1939); Friedman and White (1944), Jetter and White (1944) who analysed 34 cases—18 in a general hospital and 16 in a mental hospital. The following circumstance deserves attention in the last of the foregoing studies. The incidence of cardiorrhexis among the patients in the general hospitals did not exceed 8-11 per cent (see also the findings of Edmondson and Hoxie, 1942), whereas among the mental patients it was almost 75 per cent of cases with acute myocardial infarction (16 out of 22). It must be noted that myocardial infarction was not diagnosed in any of the mental patients because of the absence or vagueness of their complaints, for which reason only three of them were in bed, while the others continued to live as usual and were physically active.

In the overwhelming majority of cases, as most of the authors

observe, ruptures occur during the first two weeks after the onset of infarction, most commonly during the first seven to ten days (Mallory *et al.*, 1939; Diaz-Rivera and Miller, 1948; Oblath *et al.*, 1952; Wessler *et al.*, 1952; Benson *et al.*, 1958), i.e. when the processes of organization are either absent or in an incipient stage. True, several cases of later ruptures have also been described (Levine and Brown, 1929; Oblath *et al.*, 1952).

According to the findings of the Institute of Cardiology, most of the ruptures occur at the early periods of the disease and somewhat more often in women: 29 ruptures per 277 fresh infarctions in men (10.4 per cent) as against the 37 ruptures per 234 infarctions in women (15.8 per cent). Their predominance in women were first noted by Beresford and Earl (1930) and later by Wessler *et al.* (1952) and Oblath *et al.* (1952). The latter authors hold, on the basis of their angiographic studies, that the state of collateral circulation played a very important role in the occurrence of ruptures, a weak development of collaterals predisposing to them. It is from this point of view that they explain the greater incidence of ruptures in women. They maintain that owing to the milder degree of atherosclerosis in women their collateral circulation is developed weakly, and in cases of acute disturbances in coronary circulation their adaptation to the new conditions of circulation is not quite adequate. They consider hypertensive vascular disease, which occurs more often in women to be the second important factor. Jetter and White (1944), Diaz-Rivera and Miller (1948), Nesvadba (1955) also pointed out the presence of hypertension and its role in the occurrence of ruptures. The predominance of women was also observed on extensive hospital material (215 ruptures: 96 in men and 119 in women) by Mitchel and Parish (1960) who hold, however, that physical activity, administration of digitalis preparations, anticoagulation therapy and the presence of hypertension have no influence on the incidence of ruptures and that the main factor is only the extensiveness of the lesion and its transmural character. We also cannot regard hypertensive vascular disease as the decisive factor in the development of rupture: of the 66 patients with ruptures it was observed only in 21 (10 men and 11 women), i.e. in less than one-third of the cases. Interesting data are cited by Crawford *et al.* (1960). During 1957-1958 there were 600 cases of ruptures among the 3 250 000 inhabitants of London. In the middle age they were observed twice as often in men, and in older age groups in women, so that in the end the proportions were equal.

Most investigators hold that mental state plays a considerable role in the occurrence of a rupture, e.g. in mental patients who make no appropriate complaints, there are increased physical activity during the first few days following the development of infarction, elevated intraventricular pressure and strain of the ventricular wall (owing to which administration of digitalis preparations is undesirable), and, of course, the extent and character of the infarction itself.

However, some authors, Maher *et al.* (1956) in particular, believe that the role of digitalis in the development of rupture is exaggerated. The role of anticoagulants is also not clear. The materials of the Institute of Cardiology do not confirm that anticoagulation ther-

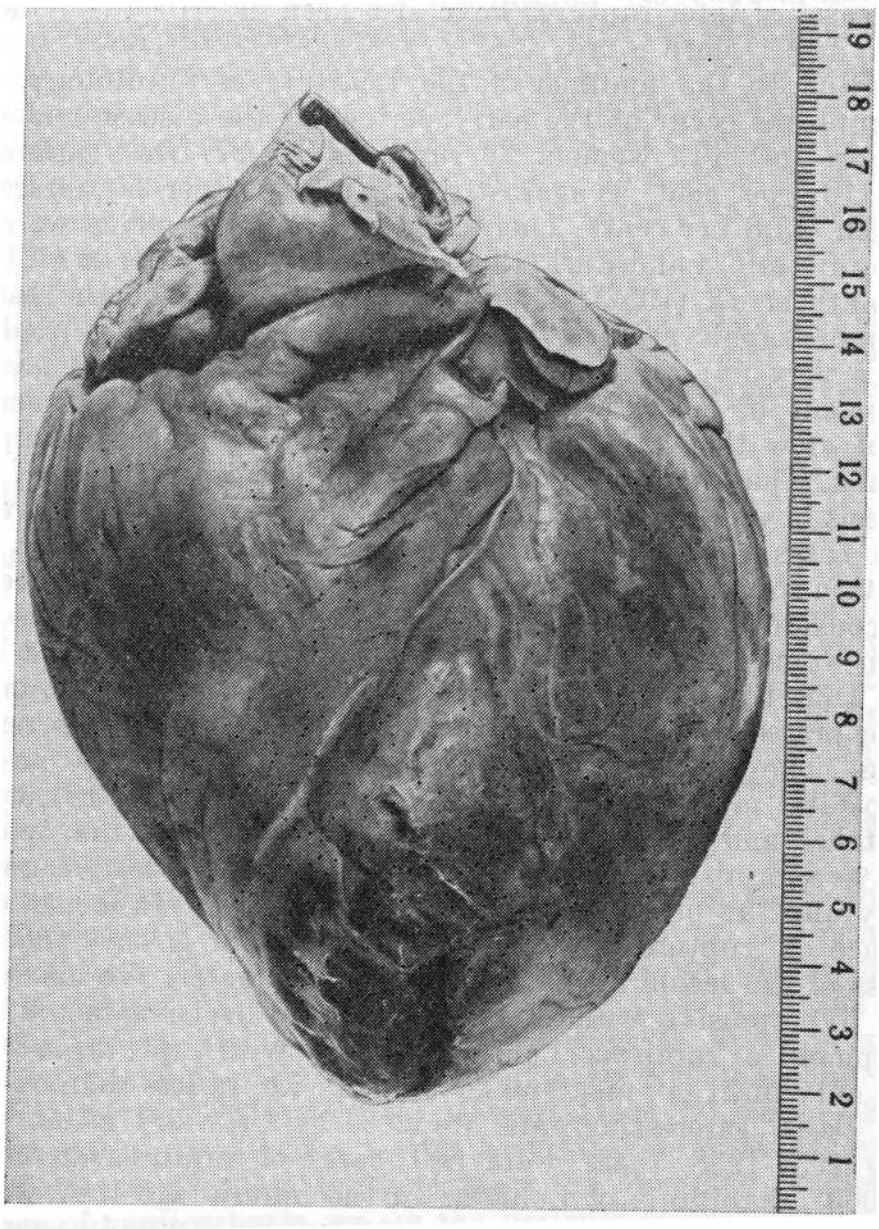

Fig. 30. Rimal rupture in the region of myocardial infarction of the anterior wall and apex of the left ventricle

apy plays a significant part in the development of this complication.

Ruptures of the heart and infarctions most commonly occur in the anterior wall of the left ventricle. According to Crawford and Mossis (1960), of 600 ruptures more than half were localized in the

anterior wall and about one-fourth in the posterior wall, while the rest of them occurred in various combinations: lateral wall, region of the apex, etc. In our observations most of the ruptures were localized in the anterior or anterolateral wall.

Macroscopically the rupture looks like a narrow fissure, usually zigzag in shape, seldom exceeding 1.5 or 2.5 cm in length (Fig. 30). In most cases it occurs at the junction of the dead and intact myocardium in the area of leucocytic reaction if the latter is already manifest. In the thickness of the myocardium the rupture is seldom of rectilinear form. Most commonly it is step-shaped because it runs through layers of the myocardium at different levels. According to Davydovsky (1958), this may indicate that the rupture does not occur all at once. This opinion is also supported by the discovery of the vast dissecting aneurysms which sometimes extend far beyond the area of the rupture, as is shown in Fig. 31. Ruptures are mainly observed during the first infarction and much less frequently during repeated infarctions. It may possibly be due to the vastness of the primary infarctions, whereas repeated infarctions are of a lesser extent. Microscopic examination shows that the edges of the infarction consist of necrotized muscle fibres, stroma and vessels abundantly infiltrated with decomposing leucocytes and layers of extravazated blood. Ruptures of the right ventricle (in accordance with the infrequency of infarctions of this localization) are observed very rarely, but their description can be found in literature just the same. According to Nesvadba (1955), 12 per cent of the patients with fresh myocardial infarction die of rupture of the myocardium of which 7 per cent (1/14 of the ruptures) are of the right ventricle.

After cardiac rupture the patient usually lives but a few minutes, rarely hours. At the same time Nesvadba mentions single cases with the patients remaining alive for up to two days. Lampesis *et al.* (1953) describe a case when the patient lived for about four weeks after the supposed rupture (he was operated on for haemopericardium). The autopsy showed a healed rupture covered with organizing thrombotic masses in the region of the apex. Hudson (1965) cites an analogous case of a patient who lived for up to six weeks.

Avulsion of the papillary muscles is another complication of the acute period. It is one of the complications that occurs much less frequently than rupture of the wall and interventricular septum, although the papillary muscles are often involved in the infarction area. Hudson (1965) who worked for several years in the field of cardiac pathology mentions only two cases of avulsion of the papillary muscles. He believes that avulsion of the papillary muscles apparently occurs more often, but in virtue of the sudden death of the patients the autopsy is performed not by a pathologist, but by a medicolegal expert.

Usually it is only one muscle that tears away, although there is a report of a case of simultaneous avulsion of both muscles. San-

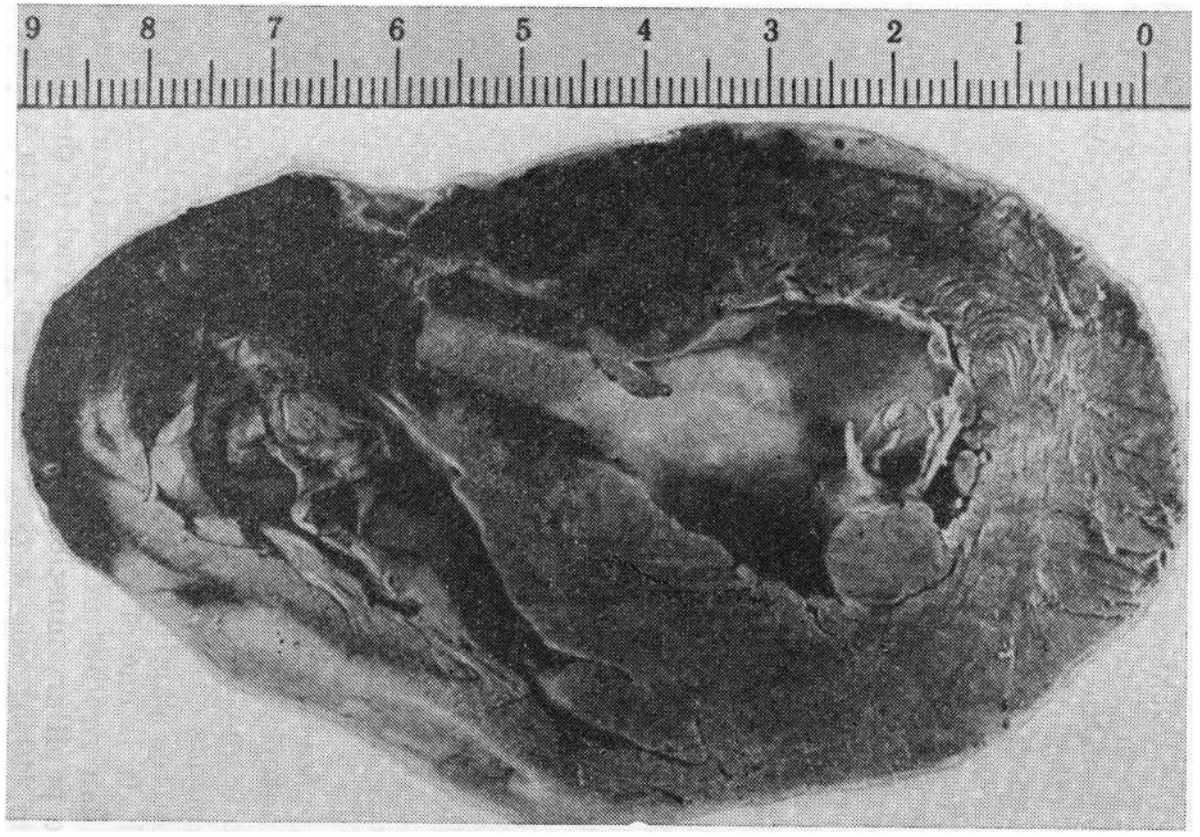

Fig. 31. Myocardial rupture in the region of infarction of the posterior wall and septum with formation of an extensive dissecting aneurysm. The rupture was apparently preceded by the formation of an acute aneurysm which is evidenced by a bay-like bulging of the left ventricular cavity

ders *et al.* (1956) cite the most extensive material of their own and sum up other descriptions of avulsion of the papillary muscles, namely, 57 cases gathered from the literature and five personal observations. According to their free data, avulsion of the posterior papillary muscle is observed six times as often as that of the anterior muscle. Only seven of the 62 cases were diagnosed during the patients' lifetime. A description of a rupture of the papillary muscle during the patient's lifetime is given by Shamov (1961). Only seven cases of the avulsion of the papillary muscles, i.e. nearly one tenth of the incidence of rupture of the left-ventricular wall, were observed in eight years in the department of pathology of the Institute of Cardiology. In most of the cases it was avulsion of the posterior papillary muscle.

Clinically avulsion of the papillary muscles is manifest as an acute mitral insufficiency, rough murmur in the region of the apex, and pulmonary oedema. The latter, according to Breneman and Drake (1962), who analysed the available literature, is the direct cause of death of 50 per cent of the patients within the first 24 hours. At the same time these authors cite two personal observations when one of the patients lived 14 and the other 11 months, which indicated the possibility of surviving the acute period of the catastrophe. Two cases, one patient living two and the other six months, are described by Askey (1950). Subsequent microscopy revealed endothelization of the avulsion surface, which to some extent confirms its remoteness.

We have been unable to find in the literature any description of avulsion of the right-ventricular papillary muscles due to myocardial infarction.

According to Edmondson and Hoxie (1942), Diaz-Rivera and Miller (1948), and Maher *et al.* (1956) a rupture of the interventricular septum occurs in 0.9 to 1.6 per cent of the cases of infarction. We observed only four ruptures of the interventricular septum in 511 acute infarctions, i.e. less than 1 per cent.

The first anatomical description of a rupture of the interventricular septum due to infarction was given by Latham in 1846. Sager (1934) cited 18 cases and pointed out that owing to its small size a rupture may often be overlooked during autopsy. To avoid this he suggests that a saline solution should be poured into the aorta before autopsy of the left ventricle and its appearance in the right ventricle watched for. One can hardly agree with this since even in the normal heart, and especially in pathological conditions, communication between the ventricles may take place through the vessels of Vieussens and Thebesius (Ozarai, 1956) and may erroneously be regarded as a microrupture.

A rupture of the interventricular septum, like an external rupture of a ventricular wall is usually observed during the first 15 days. Swithinbank (1954) gives a detailed analysis of 106 cases collected from the literature and seven personal observations; the seven rup-

tures constituted 2.2 per cent of the 318 infarctions observed by the author. The ruptures were noted somewhat more often in man (in approximately a 2 : 1 ratio), although five of the author's seven observations pertained to women, the survival of the patients ranging from several days to five years (in single cases). Schlappi and Landale (1954), however, described the longest survival in a case of a 76-year-old woman who lived to the age of 83, i.e. for seven years after the perforation. A five-year period is mentioned by Albagli and Eschar (1963). But most patients die much sooner; according to the summary data of Sanders *et al.* (1956), 50 per cent died within one week, and only 13 per cent lived for more than two months.

Hudson (1965) points out that the rupture of the septum, and also of the ventricular wall, occurs during the first infarction and in people with hypertension. After a rupture the latter may not be clinically identified, but the heavy weight of the heart indicates to its existence (Malone and Parkes, 1955). The onset of death is accompanied by the phenomena of marked right-ventricular failure. Owing to severe acute stasis of the liver symptoms of hepatic insufficiency may develop, sometimes with jaundice, the anatomical basis of which are necroses of the central parts of the hepatic lobules (Malone and Parkes, 1955). Incidentally, in rare cases this may also be observed in severe infarctions without perforation of the interventricular septum and may even be accompanied by the development of extrarenal azotaemia (Vikhert and Ushkalov, 1956).

Cardiac Aneurysm

Cardiac aneurysm is another complication of myocardial infarction. Acute, subacute and chronic aneurysms are distinguished. This differentiation is rather conditional and actually corresponds to the particular stage in the course and healing of the infarction and postinfarctional cardiosclerosis. An acute aneurysm is a bulging of the wall of a cardiac ventricle in the infarction area due to the fact that the dead area loses its natural tonus and contractility. In this place the wall of the cardiac ventricle becomes soft and flabby. The wall of an acute aneurysm is essentially the area of myocardial infarction in its acute stage, and the description of the early changes occurring up to 10 or 14 days of its existence, to the point of rupture in this area, is quite applicable to it.

The idea of subacute and chronic cardiac aneurysm is in a large measure associated with the names of Cohnheim (1881) and Marie (1896) who formed the idea of myocardial fibrosis on the basis of coronary thrombosis and coronary sclerosis.

In 1905 Hall (cited by Gornak, 1967), who accumulated extensive material for its time (112 cases of cardiac aneurysm) held that the origin of aneurysm was connected with coronary endarteritis, while in 1914 Sternberg explained the origin of the overwhelming majority of aneurysms by coronary sclerosis.

The main factor conducive to the development of aneurysms is primarily the size of the infarction itself. Extensive infarctions involving one or two contiguous walls of the left ventricle, transmural ('through') infarctions mainly serve as the background against which first an acute and subsequently subacute and chronic cardiac aneurysm develops. Precisely such infarctions are the source of the extensive diffuse or saccular aneurysms. Of course, smaller infarctions may also cause the development of an aneurysm, but in most cases they apparently lead to the appearance of so-called silent (according to Ognev's terminology) aneurysms which are essentially a thinning of the ventricular wall. Some authors (Gornak, 1967) assume that a small, at first silent aneurysm may subsequently become diffuse or saccular, but we consider that such development of the process is hardly often possible.

Another unfavourable factor contributing to the development of aneurysm, to which most authors attach considerable importance, is failure to observe a regimen of rest during the early periods of infarction (Kogan and Zharkovskaya, 1950; Schlicher *et al.*, 1954; Ezerietis, 1959; Tokareva, 1959; Nesterov *et al.*, 1963). But even complete observance of the regimen does not always prevent development of the aneurysm, especially in cases of vast infarctions (Schert and Boyd, 1955; Kogan, 1958 and Nesterov *et al.*, 1963) and severe coronary atherosclerosis which unfavourably affects the reparation processes and development of an adequate fibrous scar.

Experimental data seem to confirm this point of view. Thus in experiments on dogs involving ligation of the anterior descending branch of the left coronary artery and subsequent myocardial infarction in the anterior wall of the left ventricle Sutton and Davis (1931) observed the development of an aneurysm, if the animals were forced to run in a treadmill on the second or third day after the ligation. When the animals began to run on the sixth day no aneurysms developed. Nesterov *et al.* (1963) and Gornak (1967) obtained analogous results.

Lastly, as most of the authors note, hypertensive vascular disease considerably increases the possibility of development of an aneurysm both in experiment (Gornak, 1967) and in man, since under these conditions the intraventricular pressure is elevated and prerequisites for the early dilatation of the necrotic myocardium are created (Volynsky, 1949; Shpirt, 1953; Dodashvili, 1956; Meerzon, 1963; Nesterov *et al.*, 1963). The opinion of Brams and Gropper (1940) that hypertrophied and thickened myocardium of the left ventricle possesses greater resistance to pressure in cases of hypertensive vascular disease now has no supporters. Moreover, Shpirt (1953) and Moyer and Hiller (1951) regard the hypertrophied muscle as one of the conditions for the development of aneurysm since hypertrophied myocardium retains its ability to maintain intraventricular pressure at a high level.

The diameter of the aneurysms may range from two or three to

six or seven cm and more (Ellman, 1904; Ball, 1938; Jacobs and Elliott, 1955; Dikareva, 1959; Gornak, 1967). Aneurysms may be of the most diverse forms, but most commonly they are oval, semicircular or scyfiform (Fig. 32). The transition to the ventricular wall may be gradual and smoothed out, especially in fibromuscular aneurysms (see below). Less frequently the border is well defined, particularly on the inner surface when the entrance to the aneurysm may be annular or oval.

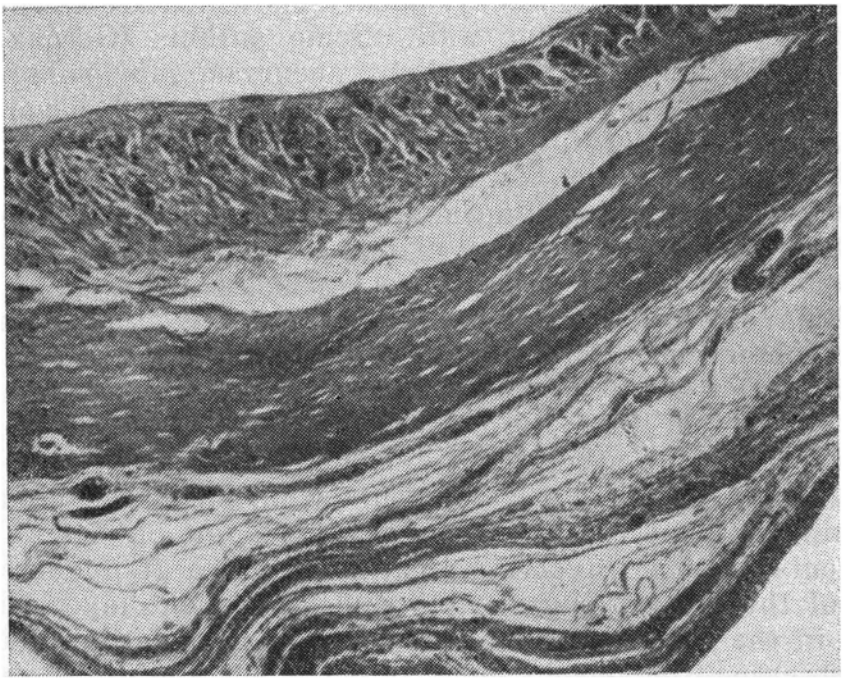

Fig. 32. Wall of a chronic aneurysm consisting of hyalinized connective tissue. An intact layer of subendocardially arranged muscle fibres is seen above. Stained with haematoxylin-eosin. Magn. x250

During the subacute period of myocardial infarction (third to eighth weeks of the disease) the structure of the aneurysmal wall differs but little from of a cicatrising infarct. A detailed description of this stage is given in Gornak's (1967) work. A thickening of the endocardium through oedema and slight fibroblast and histocyte infiltration, and accumulation of acid and later also neutral mucopolysaccharides, as is usually the case in young and maturing connective tissue, are observed. Newly formed reticular, collagenous and elastic fibres appear, i.e. the process begins that terminates by secondary endocardial fibroelastosis of the aneurysm. Early in this period remains of necrotized muscle fibres in different stages of resorption (see above), separate intact muscle fibres and whole layers of them, especially at the periphery of the aneurysm and in the area of the transition of its wall to the intact portions of the

ventricular wall, are seen in the wall of the aneurysm. The newly formed connective tissue that replaces the dead portions of the myocardium are of a different degree of maturity, depending on the time elapsed after the death of the myocardium. It is usually more mature at the periphery with newly formed fibrous structures, and is younger, rich in fibroblasts with an abundant content of RNA and acid mucopolysaccharides in the interstitial substance in the central parts. The pericardium in most cases (and in transmural infarctions, as a rule) exhibits reactive changes in the form of vascular hyperaemia, exudation of fibrin with phenomena of its organization, and proliferation of connective-tissue cells, which leads to a thickening of the epicardium and formation of adhesions with the pericardium.

The wall of a chronic aneurysm mainly consists of dense scar tissue which, unlike the young connective tissue of the early period of the aneurysm, has a regular structure. Depending on whether or not there are any muscular elements the wall may be purely fibrous or fibromuscular. Fibrous aneurysms are usually better delimited from the intact muscle of the left ventricle, whereas fibromuscular aneurysms merge with it without any sharp borders. The internal layer of the aneurysm consists of sharply thickened fibrous collagenous tissue, the bundles of intertwining fibres being, as a rule, arranged parallel to the internal surface of the aneurysm (secondary endocardial fibroelastosis). There are few vessels here; dystrophic changes of collagenous and elastic fibres in the form of their decomposition and fragmentation, and impregnation of the tissues with plasma proteins are often observed; this may apparently be regarded as evidence of the progressive enlargement of the aneurysm. The middle layer consists of alternating strata of coarse collagenous fibres, often hyalinized and also arranged parallel to the free surface of the aneurysm. Fibromuscular aneurysms have a number of layers of intact muscle fibres. Usually there are more of them in the peripheral parts of the wall, whereas the centre consists of scar tissue sometimes as thin as a sheet of oil-paper. The ratio of scar and muscular tissue may vary, the layers of collagenous and muscle fibres of various thickness alternate, being superimposed on each other in different proportions. The muscle fibres may be hypertrophied or, on the contrary, atrophic with phenomena of fatty and protein dystrophy, fuchsinophilic degeneration, in a state of necrobiosis and total necrosis.

The number of vessels in chronic aneurysms is usually reduced, especially in the central fibrous part. Gornak (1967) distinguishes three types of vascularization of the aneurysmal sac: (1) with an insignificant reduction of the number of vessels; (2) with a sharp reduction; (3) aneurysms almost totally devoid of vessels. The first type is characteristic of acute and 'young' fibromuscular aneurysms, the last two—of older aneurysms (Fig. 33) in which radiographs show vessels filled with a contrast medium only at the periphery.

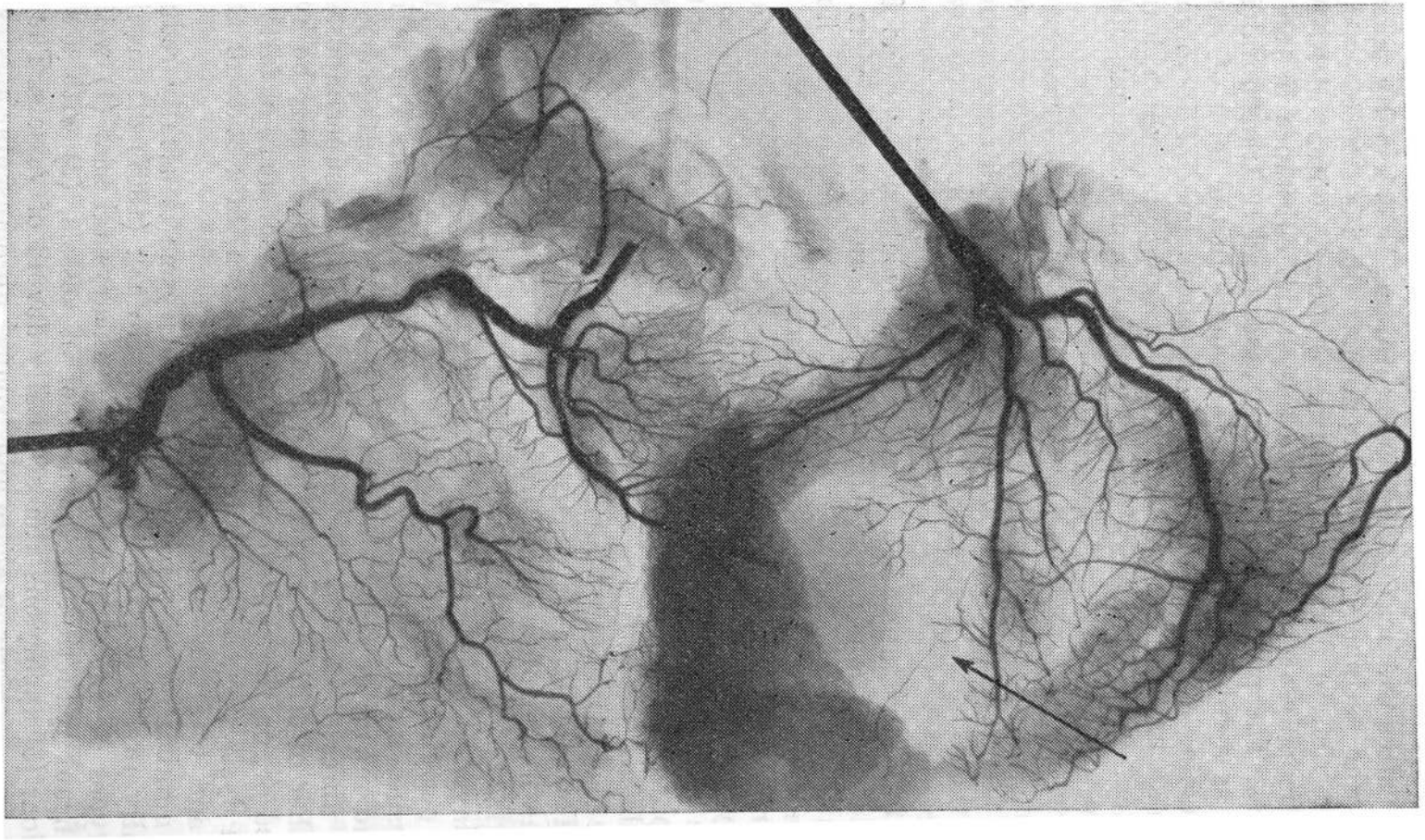

Fig. 33. Angiography of an aneurysm. Total absence of vessels in the central part of the aneurysm

In 'young' aneurysms there are many sinusoid-type vessels (Ganulich, 1967) which are subsequently partly obliterated and partly reconstructed (an elastic membrane and a muscular layer form in them). Some vessels become converted into obturator-type arteries. In Ganulich's opinion, an important part in the blood supply to the aneurysm is played by the vessels of Vieussens and Thebesius, which by interlocking with the newly-formed vessels may form a fairly dense network. However, the pre-existing vessels are subsequently progressively obliterated, thrombotic processes in the cavity of the aneurysm occlude the ostia of the Thebesius vessels, and the entire vascular network diminishes, thereby leading to the development of aneurysms with a circulation of the second and third types (according to Gornak, 1967). Since the blood vessels in the aneurysm are arranged radially and are much fewer in the central part, supply of the preserved muscle fibres in this area is considerably disturbed and all the dystrophic and necrobiotic changes are more strongly pronounced there. The result of the atrophy and death of the muscle fibres is that the fibrous central part gradually extends to the periphery and becomes increasingly more dilated. The sclerotic processes intensifying in due course in the large and small branches of the coronary vessels finally lead to metabolic disturbances in the peripheral parts of the aneurysm, atrophy and disappearance of the muscular elements, i.e. the evolution of the aneurysm always proceeds in one direction—progressing of the process.

Fatty tissue often forms in the wall of the aneurysm, mainly around the vessels in the subepicardial layer. This may not be a new tissue, but remains of the fat that forms part of the epicardium. Deposits of calcium salts in the aneurysmal wall may be seen less frequently (Hanbury, 1927; Naumann, 1947; Ganulich, 1967 and Gornak, 1967); this sometimes lends the aneurysm the character of a stony formation. In some cases bony tissue forms at the sites of calcium salt deposits. Superimposition of thrombotic masses is often observed on the endocardium in the cavity of the aneurysm, and in the infarction area (Phares *et al.*, 1953; Nesterov *et al.*, 1963; Ganulich, 1967 and Gornak, 1967, etc.). In the early periods of their existence these masses are loose, easily break away, crumble, later become indurated, structureless and hyalinized, but their organization on the part of the endocardium is feebly marked due apparently to the fibrous changes in the latter. In old aneurysms, owing to recurring waves of thrombosis, the thrombotic masses have a lamellar structure.

Some authors (Dikareva, 1964; Gornak, 1967, and Ganulich, 1967) regard a number of morphological pictures in the aneurysmal wall as a reflection of compensatory-adaptive processes. Gornak ascribes to them: (1) the secondary endocardial fibroelastosis; (2) the presence of fatty tissue in the wall of the aneurysm; (3) hypertrophy of the intact muscular tissue; (4) reconstruction of the vascular network—

formation of collaterals, obturator-type arteries and phlebectasia; (5) formation of extracardial vascular anastomoses in pericardial adhesions, and (6) existence of parietal thrombosis. One can agree with points 1, 2, 3 and 5, but points 4 and 6 are contestable since it is hard to conceive the compensatory role that the obturator-type arteries can play or the few collaterals in the aneurysmal wall, which, moreover, quickly diminish. It is rather the interlocking of the Thebesian veins with the vascular system of the aneurysm noted by Ganulich that plays a more important part in the compensation of blood circulation. The thrombotic superimpositions cannot strengthen the aneurysmal wall because the masses of the thrombus are loose at first. It is rather the processes of calcification in the aneurysmal wall that can be considered from this point of view, but they far from always take place.

At any rate all these compensatory-adaptive mechanisms in most cases cannot ensure stable aneurysmal formation or prevent its progress. Areas or foci of young connective tissue scattered in the rough scar tissue of the aneurysmal wall indicate the process of steady increase in the size of the aneurysm. Their emergence is apparently connected with fresh necroses of muscular layers retained in its wall.

Thromboembolisms

Thromboembolism is a complication of myocardial infarction and postinfarction cardiac aneurysms. The incidence of this complication ranges widely, as shown by clinical data, from 12.2 or 15 to 37.4 per cent (Allen *et al.*, 1955; Kushelevsky, 1955, and Raevskaya, 1960). Thromboembolisms may occur both in the systemic and pulmonary circulations. The source of embolisms in the systemic circulation are thrombotic superimpositions in the cavity of the left ventricle in the infarction area, or thrombi formed between the trabecular muscles owing to weakened circulation and disturbances in blood coagulation which often occur in patients with myocardial infarction, and in cases of aneurysm in the aneurysmal sac. Embolisms in the systemic circulation may result in gangrene of the extremities and intestine, splenic and renal infarctions, and disturbances in cerebral circulation with a corresponding clinical picture. The thrombo-embolic complications in the pulmonary circulation may be of two types (1) thromboembolism of the pulmonary artery, and (2) thrombosis of branches of the pulmonary artery. In both cases, however, they are associated with circulatory disorders of a congestive character. In the first case it is a matter of formation of marantic thrombi most commonly in the system of pelvic veins or deep veins of the legs with their subsequent avulsion and transportation to the main trunk or large branches of the pulmonary artery, which usually ends in death in a few seconds or minutes. In the second case local thrombi are formed in the smaller

branches of the pulmonary artery and are followed by pulmonary infarctions, as is usually the case in cardiac decompensation of any aetiology.

Dressler's syndrome. In 1956 Dressler described the so-called postinfarction syndrome: fever, pericarditis or pleurisy (Fig. 34), sometimes with a haemorrhagic exudate, pneumonia with sanguinous sputum. The changes do not usually develop before the 10th-14th day of the onset of the disease, but may also appear in the course

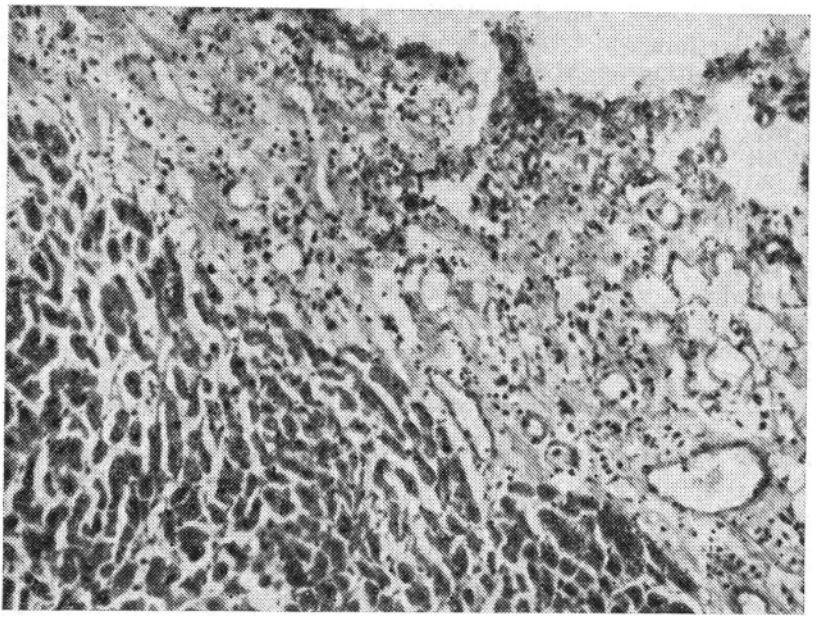

Fig. 34. Fibrinous pericarditis. Stained with haematoxylin-eosin. Magn. x100

of two years after infarction. Auto-immune origin of this complication is assumed.

Infarction of the right ventricle. The infarction of the right ventricle may be observed alone or in combination with that of the left ventricle, i.e. as an extension of the latter to the right half of the heart.

Infarction of the right ventricle occurs very seldom, although the data cited by various authors differ considerably. Table 1 presents data on the incidence of isolated and combined infarction of the right ventricle which we have found in literature and obtained by studying the results of autopsies performed in the department of pathology of the A. L. Myasnikov Institute of Cardiology.

From the Table it follows that isolated infarctions of the given localization do not exceed 1.25 per cent of the total number and, although combined infarctions of the left and right ventricles occur eight times as often, their total does not exceed 10.51 per cent of infarctions of the left ventricle. These figures are close to those

Table 1. Incidence of Isolated and Combined Infarctions of the Right Ventricle

Authors	Year	Number of infarctions		
		Total	Isolated of the right ventricle	Combined infarction of the right and left ventricles
Saphir *et al.*	1939	54	1	—
Wang *et al.*	1948	556	10	—
Wartman, Hellerstein	1948	253	4	18
McDonald and Bentley	1951	100	1	—
Slapak	1953	351	5	49
Wright *et al.*	1954	89	1	17
Halpern *et al.*	1956	195	4	12
Shamesova	1956	141	1	14
Goder	1960	752	9	146
Strasser	1963	224	2	20
Roubelakis *et al.*	1965	502	8	—
Roubelakis *et al*	1966	364	—	40
Data of Institute of Cardiology (USSR Academy of Medical Sciences)		959	6	34
Total: isolated		4176	52 (1.25 per cent)	—
Total: combined		3328	—	356 (10.51 per cent)

cited by Wartman and Hellerstein (1948) (1.7 per cent of isolated infarctions of the right ventricle), but are 50 per cent lower than those of Halpern and Weinberg (1957) (3 per cent).

A description of individual cases of isolated infarctions of the right ventricle can be found in the works of Nedlina *et al.* (1962) and Vinogradova *et al.* (1967). Wade (1959) gives a description of eleven of his own observations and nine collected from literature. Retrospectively surveying 1651 cases of myocardial infarction Zaus and Kearns (1952) discovered four authentic isolated infarctions of the right ventricle and added one of their own observations and seven taken from literature, i. e. analysed 12 cases.

To explain the infrequency of infarctions of the given localization, various arguments are used, but it must be admitted that most of them have their 'pros' and 'cons'.

An assumption was voiced (Blumgart *et al.*, 1940) that the blood supply to the right ventricle in cases of impaired coronary circulation can be compensated from its cavity through Thebesian vessels. It was shown, however, that the Thebesian vessels can be filled from the cavity of the right ventricle only if the intraventricular pressure equals that in the cavity of the left ventricle, which is possible only in cases of inborn defects (defect of the interventricular

septum) or pulmonary heart (Eckstein *et al.*, 1941). Moreover, Prinzmetal *et al.* (1948) showed in experiment that arterial and not venous blood flows to area of ischaemia. In the opinion of Laurie and Woods (1962), the predominantly subendocardial localization of infarctions of the right ventricle, which they observed, disproves the role of the Thebesian vessels. Today there are no reasons whatsoever to regard the Thebesian vessels as a factor accounting for the infrequency of right ventricular infarctions.

The following circumstances are of considerable importance. It was shown (Prinzmetal *et al.*, 1948) that the blood flow through the intercoronary anastomoses from the left coronary artery to the right is three times that in the opposite direction. The importance of collateral blood supply from the system of the left coronary artery is also emphasized by the fact that infarctions of the right ventricle are often combined with and conditioned by the stenosing atherosclerosis or occlusive thrombosis of the left anterior descending or left circumflex artery. The incidence of infarctions of the right ventricle (3.13 per cent), according to Meciani and Tomasini (1966), does not coincide with that of thrombosis of the right coronary artery (which, according to their data, is thrombosed in 22.5 per cent of cases, i.e. seven times as often as the observed number of infarctions).

In 1928 Wearn showed that the correlation between the capillary bed and the muscle fibres was the same on the right and left. At the same time, according to Gregg (1950), the left ventricle does three times as much work and is under much worse conditions as regards reserve potentialities in anoxia. Normally these reserve potentialities are quite sufficient to do the work, but in conditions of stenosing atherosclerosis the 'coronary reserve' is not adequate to the demands made of the left ventricle, and an infarction develops, whereas at relatively the same level of blood flow the right ventricle is not affected. A better tolerance of ischaemia by the right ventricle and the importance of the blood flow through anastomoses from left to right is also indicated by the absence of infarction of the right ventricle in cases where the right coronary artery arises from the pulmonary artery (Jordan *et al.*, 1950). On the contrary, such an anomaly as the rise of the left coronary artery from the pulmonary artery often leads to myocardial infarction of the left ventricle already at a young age.

The following suggestion, very essential in our opinion, is made: during systole the thick-walled left ventricle compresses the intramural arteries and thus deprives itself of the inflow of blood through the usual vessels, and also through collaterals and anastomoses, whereas in the right ventricle with its thin wall this is not observed, and during systole its muscle fibres continue to receive blood (Büchner, 1939; Gregg, 1950; Wiggers, 1954, and Müller, 1962). In virtue of the latter circumstance a number of authors call attention to the fact that infarction of the right ventricle is most commonly

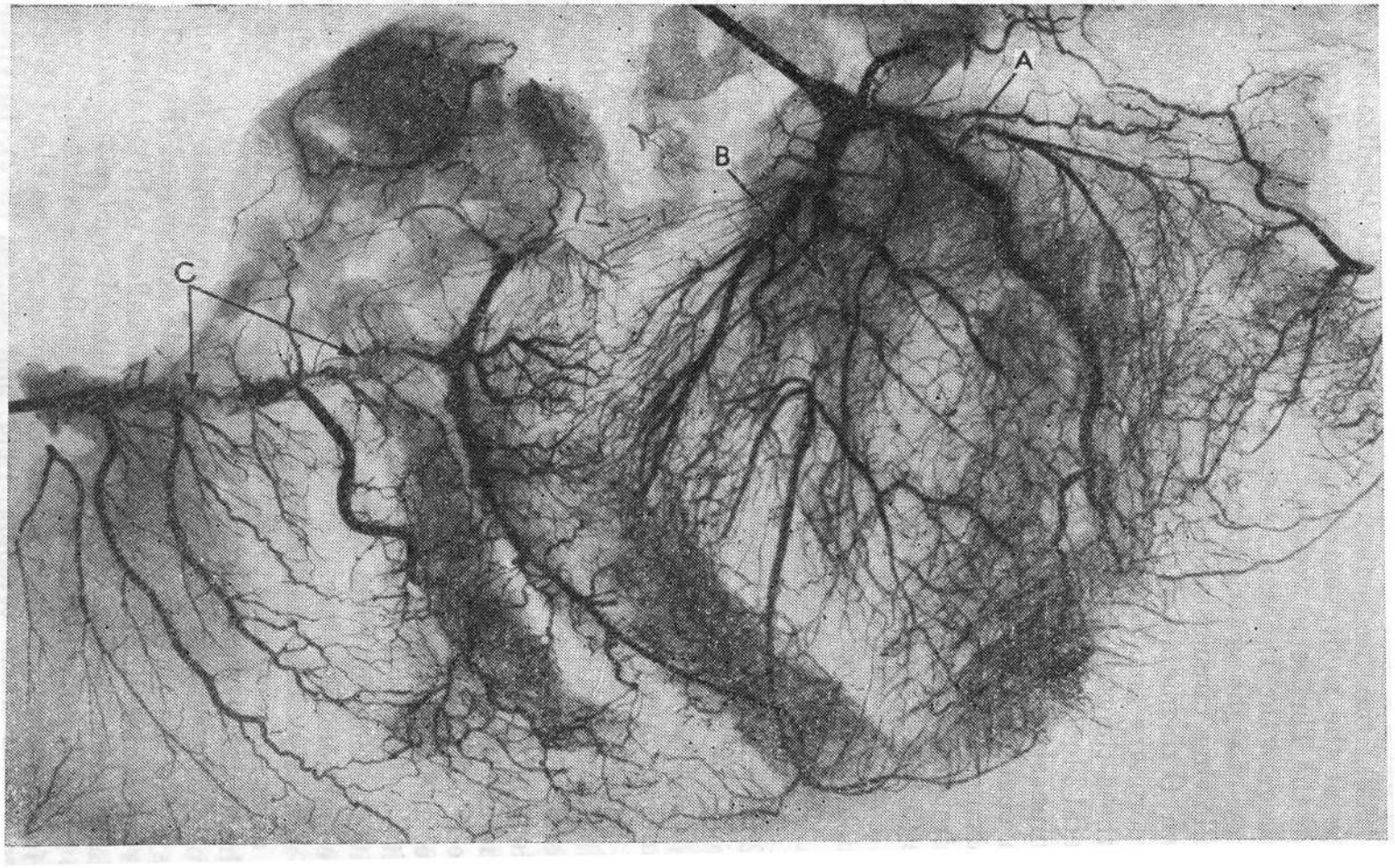

Fig. 35. Stenosis of the circumflex branch of the left coronary artery (*A*), obliteration of anterior descending branch of the left coronary artery (*B*), thrombosis of the right coronary artery (*C*) in a case of infarction of the posterior wall of the right ventricle

observed in cases of its hypertrophy (Vinogradova *et al.*, 1957; Wade, 1959, and Roubelakis *et al.*, 1965); however, not everybody agrees with this (Meciani and Tomasini, 1966).

In the overwhelming majority of cases infarction of the right ventricle occurs on the background of severe stenosing atherosclerosis of the main branches of coronary arteries (Fig. 35). In cases of stenosis of the right coronary artery thrombosis in the system of the left coronary artery may lead to infarction of the right ventricle, since the main anastomoses supplying the wall of the right ventricle are excluded, and, contrariwise, in cases of stenosing atherosclerosis in the anterior descending and circumflex arteries fresh thrombosis of the right branch may produce a similar effect (condition the development of infarction of the left ventricle) in virtue of the failure of the right-to-left anastomoses.

According to most authors, the posterior wall is the most common localization in infarctions of the right ventricle. Galakhov's data (1970) based on an analysis of autopsies at the Institute of Cardiology for ten years show that in combined infarctions the posterior wall is affected twice as often as the anterior, while affection of the anterior wall is most commonly observed in isolated infarctions. In the cases under consideration infarctions of the posterior wall were combined more often with thrombosis of the right coronary artery, infarctions of the anterior wall with thrombosis of the anterior descending artery. Infarctions of the lateral wall and the region of the apex of the right ventricle are less frequent. In combined infarctions the affection of the posterior part of the septum and the adjoining parts of the posterior walls of the right and left ventricles is the most typical.

In some cases the infarction of the right ventricle is combined with the infarction of the right atrium, which can be explained by the fact that the latter is supplied with blood by the right coronary artery (Nedlina *et al.*, 1962). Transmural infarctions are observed in most of the cases, subendocardial infarctions are less frequent.

2

PATHOGENESIS

Myocardial infarction is an ischaemic necrosis of the heart muscle caused by an acute insufficiency of the coronary blood flow. The insufficiency may result from a sudden cessation of the inflow of arterial blood through the coronary vessel or of a disparity between the oxygen requirement of the myocardium and the ability of the coronary arteries to meet it. According to Myasnikov *et al.* (1963), coronary and noncoronary necroses of the myocardium are distinguished. Necroses of the myocardium of noncoronary origin are considered a result of metabolic disturbances in the heart muscle due to the action of electrolytes, hormones, toxic products, infections, etc. Necroses of coronary origin are the changes in the myocardium due to disturbances in coronary blood circulation. Myocardial infarction is thus always a necrosis of coronary nature.

Although the pathogenesis of myocardial infarction has been studied for almost 100 years, in many respects it is not clear as yet. Numerous pathological studies leave no doubt that the anatomical basis of myocardial infarction is coronary atherosclerosis. Atherosclerotic changes in the vessels of the heart are practically always found in myocardial infarction; in most of the cases the manifestations of atherosclerosis are severe, with stenosis and often obliteration of the lumina of the coronary arteries. Strukov *et al.* (1967) found severe coronary atherosclerosis in the cardiac vessels in 97-98 per cent of infarctions. Anichkov *et al.* (1957) revealed severe coronary atherosclerosis in 89 per cent of 446 infarctions, and only in 3 per cent they did not find atherosclerotic changes in the coronary arteries. It should be noted that in cases of infarction atherosclerosis is found not only in elderly, but also in young people (aged from 18 to 39 years), as is shown by the data of Moritz and Zamcheck (1946); Yater *et al.* (1951), and others.

Of the 960 patients who died of myocardial infarction at the Institute of Cardiology in the last ten years advanced atherosclerosis with stenosis of the coronary arteries was observed practically in all of them. Today most investigators do not doubt that myocardial infarction occurs in connection with coronary atherosclerosis. It should be pointed out, however, that in 2-4 per cent of cases myocardial infarction was observed without marked atherosclerotic changes in the coronary arteries (Smoliyannikov and Apatenko, 1956; Anichkov *et al.*, 1957, and Strukov *et al.*, 1967). Sometimes people who died suddenly are included in the group of patients with myocardial infarction. It is known that in cases of sudden death atherosclerotic changes in the coronary arteries are found much less frequently than in myocardial infarction. No atherosclerotic changes in the heart vessels are found in more than 10 per cent of the cases of sudden death (Yater *et al.*, 1951; Smoliyannikov and Apatenko, 1956; Avdeev, 1958; Horn and Fine, 1963; Matova, 1966). We consider that the mechanism of sudden death and that of myocardial infarction somewhat differ from each other, and it is probably incorrect to identify sudden death with myocardial infarction, although their origin undoubtedly have much in common. The development of myocardial infarction is underlied by a sudden acute disturbance in coronary blood circulation in which certain factors may play part: (1) cessation of blood flow to the myocardium due to coronary thrombosis on a background of strongly pronounced atherosclerosis; (2) the same under conditions of patent, but sharply changed vessels due to an atherosclerotic process in them and stenosis of their lumina; (3) in rare cases, predominantly in young people, development of myocardial infarction on a background of moderate atherosclerosis with or without coronary thrombosis.

Myocardial infarction most commonly occurs in marked atherosclerotic changes in the heart vessels owing to occlusion of a lumen of a coronary artery by a thrombus. This classic variant of the mechanism of the development of myocardial infarction was established as early as 1909 by Obraztsov and Strazhesko who described three cases with different clinical picture of the disease in which the pathological find was one and the same, namely, atherosclerotic changes in the heart vessels and their thrombosis.

Cases of myocardial infarction associated with formation of a thrombus not on a background of atherosclerosis of the heart vessels, but owing to coronary thrombo-angiitis or (still less frequently) due to coronaritis of rheumatic aetiology are extremely rare. The appearance of myocardial infarction owing to embolism with thrombotic masses from the affected cardiac valves or thrombotic superimpositions detached from the parietal endocardium or from an auricle of the heart, from the operative field during surgical intervention, etc., is described as casuistics. For example, we observed a case where myocardial infarction developed on a back-

ground of atherosclerotic changes in the coronary arteries owing to a dissecting aneurysm which led to the formation of a haematoma at the ostium of a coronary artery.

As to the significance of thrombosis of the coronary arteries in the onset of myocardial infarction the data are very contradictory. As Table 2 shows, the incidence of thrombosis in myocardial infarction ranges very widely—from 30 (Branwood and Montgomery, 1956, and Smoliyannikov and Apatenko, 1956) to 92 per cent (Thomas *et al.*, 1963).

It should be emphasized, however, that most of the reports of clinicians and pathologists based on extensive material, e.g. the data published by Davydovsky (1958); Lukomsky and Tareev (1958), and Strukov *et al.* (1967) mention a high incidence (70-80 per cent) of thromboses in myocardial infarction. The differences between the data of various authors may in large measure be due to the factor of fortuity. This possibly accounts for the fact, for example, that Smoliyannikov and Apatenko found thrombosis only in 31 per cent of myocardial infarctions. Later, on the basis of pathological studies of young people with feebly marked atherosclerosis Smoliyannikov and Naddachina (1963) reported that myocardial infarction 'is accompanied, almost as a rule, by an occlusive thrombus in one of the major arteries'.

Table 2. Incidence of Coronary Thrombosis in Myocardial Infarction

Authors	Year	Number of myocardial infarctions	Incidence of thrombosis
Lisa, Ring	1932	32	13 (40.7%)
Appelbaum, Nicolson	1935	150	113 (75.3%)
Bean	1938	300	240 (80%)
Gross, Sternberg	1939	153	116 (75.9%)
Yater *et al.*	1948	114	79 (69.3%)
Anichkov *et al.*	1956	446	311 (75%)
Branwood, Montgomery	1956	108	35 (33%)
Shamesova	1956	141	108 (76.4%)
Smoliyannikov, Apatenko	1956	305	95 (31.2%)
Strukov *et al.*	1959	144	102 (70%)
Ehrlich, Shinohara	1962	130	57 (43.8%)
Horn, Fine	1963	141	64 (45%)
Thomas *et al.*	1963	129	119 (92%)
Meadows	1965	100	30 (30%)
Smoliyannikov	1967	32[1]	Almost as a rule
Naddachina		86	51 (60%)
Institute of Cardiology	1968	511	191 (37.4%)
Total		2990	1724 (57.7%)

1) The authors cite no figures, but merely point out that the patients were under 40 years of age and had feebly marked atherosclerosis, but, almost as a rule, with occlusive thrombosis of one of the coronary arteries.

But even if we consider the contradictory data and the mean incidence of thrombosis, we shall find thrombosis to be the cause of myocardial infarction in half the cases. What factors then bring about the development of thrombosis in atherosclerosis? There are undoubtedly two leading factors: impaired smoothness of the vascular wall and a change in the thrombogenic properties of the blood.

Wartman *et al.* (1956) and Paterson (1961) link the acute disturbance in coronary circulation with a massive haemorrhage into the atherosclerotic plaque and subsequent thrombosis of the coronary arteries. Conditions for thrombus formation are created similarly by crumbling of the atheromatous masses of the plaque into the arterial lumen with development of a thrombus in this area (Khamitov, 1956). Such cases, however, are extremely rare.

The mechanism of thrombus formation in a coronary artery is more complex than a mere precipitation and decomposition of formed elements on the vascular wall, as some old authors believed (Anichkov *et al.*, 1956, and others). Experimental, clinical and pathomorphological observations have demonstrated the complexity of the mechanisms of thrombus formation which appears to be a result of an aggregate of anatomical, functional and biochemical disturbances connected with the state of the whole organism.

We should like to emphasize a close relationship between the general and local changes. In connection with recent advances in studying the general patterns of the alterations in the thrombogenic properties of the blood there has been a tendency to underrate the role of local changes in the vascular wall in the pathogenesis of thrombosis. Some authors ignore the significance of the changes in the area of atherosclerotic plaque, the significance of the changes in the enzymes in the vascular wall taking part in coagulation and preventing thrombus formation, as, for example, the fibrinolytic activity of the vascular wall. It goes without saying, however, that the mechanism of thrombus formation in a coronary vessel can be elucidated only by a combined study of the general and local factors.

In speaking of the general changes as factors contributing to the development of myocardial infarction it is first of all necessary to dwell on the changes in the thrombogenic properties of the blood and the reasons for these disturbances in atherosclerosis. During the last decade the scheme of thrombus formation has suffered great changes and is being continuously ascertained. Only one thing is clear, i.e. that in the system of thrombogenesis it is possible to distinguish factors which condition blood coagulation, i.e. coagulants, and factors which prevent this coagulation or even cause lysis of the precipitating fibrin.

In the studies of the 1950s concerning the biochemical essence of pathological thrombogenesis the authors dealt mainly with the role of coagulating factors in the development of thrombosis. These studies were of certain importance because they made it possible to elucidate the part played by thrombin, prothrombin, factors

V and VII, the thromboplastic activity of the blood, and antihaemophilic globulin in the development of thrombosis. But as is often happens, these studies were the reason for the appearance of the orthodox point of view on thrombosis as a result of an increased content of coagulants. An increase in the content of prothrombin was regarded as late as 10 to 15 years ago as an indication of a prethrombotic state. At the same time numerous experimental and clinical observations showed that even a very high content of such coagulants as prothrombin, thrombin, factor V, etc. does not necessarily lead to development of a thrombus in the vessels. For example, an increase in the content of prothrombin in the blood to 180 per cent effected by Kudryashov *et al.* (1964) did not produce a thrombus in the vessels of a rat. The studies of Kudryashov *et al.* (1964) are well known in which thrombin, one of the end enzymes responsible for blood coagulation, was administered into the circulation. Its administration to healthy animals produced no thrombus. Moreover, the blood usually lost its ability to coagulate. On the other hand, according to numerous clinical observations (Konyaev 1959; Pollard *et al.*, 1962 and others), thrombi formed in cases of a low prothrombin content of the blood and even on a background of haemorrhagic diathesis.

It proved impossible to explain the appearance of thrombi in the coronary arteries by an increase in the content of coagulants alone, and therefore of late the researchers have turned their attention to anticoagulation factors. It is known that the blood contains a considerable amount of heparin and possesses fibrinolytic activity. This combination of heparin and fibrinolysin not only prevents the formation of fibrin; fibrinolysin catalyses the digestion of fresh filaments of fibrin. The function of the anticoagulation system of the organism—prevention of pathological thrombogenesis—is an indispensible condition theoretically substantiated by Kudryashov *et al.* (1964).

A healthy organism responds with an anticoagulation reaction to the appearance of any conditions which enhance thrombogenesis, e.g. an increase in the content of factors contributing to coagulation, changes in the vessel wall due to its injury, etc. This reaction consists in an increased content of heparin and heightening of fibrinolytic activity of the blood, which compensate for the changes and thereby prevent thrombogenesis. The anticoagulation reaction can be demonstrated in Kudryashov's classical experiment with administration of prothrombin into the blood circulation, in response to which the content of anticoagulants in the blood and its fibrinolytic activity in healthy animals increase.

Our observations conducted in 1959-63 showed that in atherosclerosis this compensatory anticoagulation reaction is considerably diminished and in some cases is absent. We formed such conjectures for the first time in examining rabbits with experimental atherosclerosis when in response to administration of thrombin into the cir-

culation we could not obtain the reaction that occurred on administration of this preparation to healthy animals. Further clinical observations confirmed that in the development of atherosclerosis not only the content of free heparin in the blood and the fibrinolytic activity decrease but also the chances for their compensatory increase diminish, i.e. conditions are created for pathological thrombogenesis. These experimental and clinical observations were subsequently corroborated by certain authors and are now generally accepted (Panchenko, 1956; Yaroshevsky and Zhavoronkova, 1962; Andreenko, 1967; Janushkevichus, 1970, and others).

While studying the causes of the diminished effectiveness of the anticoagulation reaction in atherosclerosis, we noticed peculiarities in the local changes in the vessels. To begin with, it is necessary to dwell on the significance of the changes in the heparin content in the blood. As is known, heparin is secreted by mast cells found in large numbers around the vessels in the lungs, the liver, and the skin, in coronary vessels, etc. As Kalishevskaya (1968) point out, the mast cells are natural humoral agents of the anticoagulation system. In people with a lower incidence of myocardial infarction and atherosclerosis, e.g. in Africans, there are twice as many mast cells in the myocardium and the skin as compared to Europeans with a much higher incidence of myocardial infarction (Fernex, 1961). Fernex and Sternby (1964) have established that in persons with marked coronary atherosclerosis and myocardial infarction there are fewer mast cells in the myocardium than in healthy people of the control group. It is known that the development of atherosclerosis in which the tendency toward thrombogenesis increases is accompanied with hypoplasia and decrease in the number of heparinocytes (Cairns and Constantinides, 1954, Ermilov, 1962).

It is for that reason that attempts to associate thrombosis of the coronary arteries with the decrease in the number of mast cells in the myocardium appeared (Paterson, 1961; Mills *et al.*, 1968 and others).

It is known that mucopolysaccharides, according to certain authors, possess marked anticoagulation properties. At the same time the development of atherosclerosis is accompanied with considerable changes in the mucopolysaccharides of the vessel wall, which may also lead to a decrease in the anticoagulant properties of some part of the vessel wall and influence thrombus formation.

Studies of the fibronolytic activity of the vascular wall reveal interesting regular patterns. Investigations of Witte and Brassel (1958); Astrup *et al* (1959); Kirk (1963); Nikitin (1967); Oborin (1967) have shown that the adventitia possesses the highest fibrinolytic activity; in the media the activity diminishes, and in the intima practically equals zero. In atherosclerosis, especially in the region of the plaque, fibrinolytic activity decreases.

According to Barta and Nagi (1961), fibrinolysis is less intensive in the region of the thrombus than in the general blood circulation.

It is also important to emphasize, as our own findings and those of other authors (Poller, 1957; Perlik, 1964) show, that during the development of atherosclerosis, when there is a tendency toward pathological thrombogenesis, the content of heparin and fibrinolysin inhibitors increases. Perlik (1964), for example, links the incidence of thrombosis in atherosclerosis with the increase in antiheparin activity of thrombocytes in the tissues. Although the reasons for the increase in antiheparin and antifibrinolytic activity of the blood in atherosclerosis are not clear as yet, an increase in both the total content of these inhibitors and their content in the tissues is conducive to thrombus formation.

The relation between the coagulation and anticoagulation factors is undoubtedly much more complicated than it is considered. The complexity of this relation is demonstrated at least by the fact that in the acute period of myocardial infarction we and other authors found in a certain percentage of cases an increase in the fibrinolytic activity and heparin content in the blood.

The studies of Nikolaeva (1961), worker of the Institute of Cardiology, have shown that such changes, even more strongly pronounced, occur in angina pectoris. In cases of pains of noncoronary origin, e.g. radicular, such changes in the heparin content or fibrinolytic activity have not been found.

Ermilov (1962), Pepler and Meyer (1962) observed hyperfunction of heparinocytes during the development of thromboses which may also be regarded as a manifestation of the protective anticoagulation that determines increased production of heparin. This reaction, however, is of a short duration and usually lasts several hours, by the end of the first or the beginning of the second day it is replaced by an increase in the thrombogenic properties of the blood through a decrease in fibrinolytic activity and in the heparin content with simultaneous increase in the content of coagulants.

It is interesting that these data on the anticoagulation reaction in the acute period of myocardial infarction are somewhat similar to the data furnished by the pathological study of the incidence of coronary thrombosis in cases of sudden death and to the data on the incidence of coronary thrombosis depending on the duration of life following the appearance of the first signs of acute coronary failure. Vikhert *et al.* (1964) found an increase in the incidence of thrombosis along with the increase in the duration of life of people who died of myocardial infarction.

As Table 3 shows, in cases of death 12-24 hours after the appearance of symptoms of coronary failure coronary thrombosis was found in 24.1 per cent. With the increase in this period the incidence of thrombosis also increased and from the third day on persisted at about the same level, approaching to the mean incidence of thrombosis in myocardial infarction.

Spain and Bradess (1960) cite almost the same data. They found thrombosis in 16 per cent of patients who died one hour after the

appearance of signs of acute coronary insufficiency, in 37 per cent of those who died in 20 hours and in 54 per cent of those who died in more than 24 hours.

Table 3. The Incidence of Coronary Thrombosis Depending on the Duration of Patients' Life

Duration of life / Myocardial infarction	12-24 hrs	up to 2 days	up to 3 days	up to 4 days	5-6 days	7-20 days
With thrombosis	20	30	32	34	38	121
Without thrombosis	63	52	29	25	32	101
% of thrombosis	24.1	36.5	52.4	57.6	52.3	54.5

Note: Death within 12 hours is considered sudden.

It is known that in cases of sudden death coronary thrombosis is a less frequent occurrence than in those of formed myocardial infarction. In analysing 115 cases of sudden death among soldiers 18-40 years old Moritz and Zamcheck (1946) found thrombosis only in 27 per cent. Rabson and Halpern (1948) cite even more convincing data: they found coronary thrombosis in 27 per cent of those who died suddenly and myocardial infarction in 75 per cent of those who had thrombosis, whereas of the 73 per cent without coronary thrombosis infarction was found only in 5 per cent. According to Naddachina (1961) fresh thrombosis was found in an average of 27 per cent of cases of sudden death, the incidence of thrombosis being much higher in people with more strongly pronounced and severe atherosclerosis. They also more frequently had a formed myocardial infarction. Smoliyannikov and Naddachina (1967) found quite a different picture in young people who had freebly marked coronary atherosclerosis, but died of myocardial infarction; most of them had coronary thrombosis. This indicates that (1) cases of sudden death differ in their anatomical manifestation from those where myocardial infarction was confirmed clinically and anatomically, and (2) acute coronary failure with sudden death is apparently due to acutely developed myocardial ischaemia which is underlied in most cases by functional factors.

These anatomical findings coincide with some peculiarities of the thrombogenic properties of the blood which are manifested in the increased fibrinolytic activity and heparin content in the blood of most patients with acute coronary insufficiency.

As far back as 1906 Morawitz wrote about high fibrinolytic activity of the blood in suddenly died patients. The blood taken from them is capable of lysing thrombi. The possibility of spontaneous lysis of thrombi not only in laboratory animals, but also in man, is no longer doubted either by experimenters or clinicians. The possibility of thrombolysis during the acute period of myocardial infarction is also confirmed by some pathological findings, in particular by the possible recanalization of the thrombus. Davydovsky (1958) pointed out that the central part of the thrombus may be destroyed in coronary thrombosis. The changes in the lytic properties of the blood and in the content of heparin probably account for fewer thromboses found in cases of sudden death and in death of patients with myocardial infarction during the first hours of the disease.

These examples show the complexity of the mechanisms of thrombus formation in the heart vessels and the relations between the coagulation and anticoagulation factors. The significance of the local factor in thrombus formation, in particular in the coronary vessels, cannot be excluded. Constantinides (1966) who conducted particularly thorough investigations in this direction by means of serial sections established rupture of the upper layers of the atherosclerotic plaque with a haemorrhage into the surrounding tissues in all cases of coronary thrombosis and convincingly documented all the ruptures by using microphotography. The size of the ruptures, according to him, seldom exceeded 1000 μ being an average of 300-400 μ, i.e. they could be easily missed without using serial sections. Moreover, in rabbits with experimental atherosclerosis of the coronary arteries and aorta he managed to produce analogous ruptures in the region of the plaque with an addition of thrombosis by combining an acute rise in blood pressure with blood coagulation. These interventions being conducted separately did not produce thrombosis.

The experiments discussed above are somewhat similar to Chazov's studies in that they emphasize the significance of the disturbances not only in the coagulation properties of the blood, but also in the local, functional or anatomical vascular factor.

Today considerable importance in myocardial infarction is attached to the change in microcirculation as a factor that aggravates the process and contributes to thrombus formation and the development of shock. A change in the properties of thrombocytes plays an important role in disturbing microcirculation. It is known that in atherosclerosis the adhesiveness of thrombocytes is disturbed, their life span decreases and the possibility of their decomposition increases, which is conducive to an increase in the content of coagulation factors (Kudryashov and Kalishevskaya, 1960; Mustard *et al.*, 1964, and Lukomsky *et al.*, 1968).

There is no doubt that certain biophysical and physico-chemical properties of the vessel wall also influence thrombus formation.

The formed elements of the blood, including thrombocytes, and also fibrin have an electric charge differing from that of the vascular intima. Injury to the vascular wall and the development of atherosclerotic changes, as the observations of Kovaleva at the Institute of Cardiology; Sawyer *et al.* (1953), and Hoppenstein *et al.* (1962) have shown, lead to change in the electrical potential of the vascular wall and a decrease in the difference of potentials between the formed elements of the blood and the vascular wall, which creates conditions for thrombus formation.

In completing the discussion of the role of thrombosis in the development of myocardial infarction under conditions of atherosclerotic affection of the heart vessels we should like to dwell on two more still debatable questions.

Some authors (Branwood and Montgomery, 1956; Khamitov, 1956, and Vikhert *et al.*, 1964) expressed an opinion that in a number of cases the 'age' of the infarction and the 'age' of the thrombus in arteries do not coincide, i.e. according to histological findings, the myocardial infarction is older than the thrombus. These data in some measure disproved the significance of thrombosis in the development of myocardial infarction. We have now, however, revised our opinion because a more detailed investigation revealed that this is only a seeming difference. In certain cases young connective-tissue cells appeared in the area of the myocardial infarction and there were no signs of organization of a thrombus. On closer examination it turned out that this took place only in cases when the thrombus formed in the region of a sharply sclerosed, hyalinized or calcified plaque almost totally devoid of cellular elements on the part of the vascular lumen. Under these conditions the delayed process of organization of a thrombus was quite natural.

The second debatable question arises in connection with the fact that in some cases there is a disparity between the area of the myocardial infarction and the reservoir of the thrombosed artery (Lapin, 1955). This may occur only in cases where there is a sharp stenosis of the arterial branch that supplies the area of the infarction, the blood supply of the latter being provided mainly through anastomoses from another branch, and it is the thrombosis of this branch that leads to the development of infarction in the reservoir of a 'foreign' artery (a so-called infarction at a distance). In most of the cases the area of infarction coincides with the reservoir of the thrombosed vessel, and, if we take the point of view that the thrombosis is secondary, we shall find it impossible to explain why thrombosis develops precisely in the reservoir of the artery which vascularizes the area of the infarction.

The second variant of the development of myocardial infarction is connected with severe atherosclerosis of the coronary vessels, but without acute occlusion of their lumina with thrombotic masses.

Severe stenosing atherosclerosis is the cause of myocardial infarction in about 35-40 per cent of the cases. The most demonstrative

and easiest to explain are the cases in which the coronary vessel is sharply stenosed by the developing atherosclerotic plaque. In our practice there was a case when myocardial infarction in a 30-year-old person was conditioned by a single plaque in the coronary artery, which sharply narrowed its lumen.

In the group of 320 patients who had died of myocardial infarction without coronary thrombosis severe atherosclerosis was found in 316 of whom 261 had stenosis with narrowing of the vascular lumen by more than 50 per cent. In such cases autopsy most commonly reveals circularly arranged atherosclerotic plaques with massive deposits of calcium salt and stenosis or even obliteration of the vascular lumina. Moreover, such a development of coronary atherosclerosis is accompanied with atrophy of muscle fibres of the vascular wall and their replacement by collagenous tissue, which finally leads to the loss of functional properties by the vascular wall.

Severe coronary atherosclerosis is attended with certain factors favouring the development of necrosis in the myocardium. In addition to a sharp narrowing of the lumen, the vascular wall loses its elasticity, which is conducive to the disturbances in the blood flow. Impairment of collateral circulation, owing to the atherosclerotic changes in the intercoronary anastomoses, is another factor that leads to the development of infarction.

Coronary atherosclerosis usually affects not a single vessel, involving, to some extent, other arteries and thereby impairing the blood supply through the intercoronary anastomoses, the circulation through which cannot be considered physiologically adequate. First, in most cases the blood circulates also through arteries affected with atherosclerosis, since isolated atherosclerosis of a single coronary artery hardly ever occurs, and the other arteries also have changes which limit their functional potentialities. Second, as the studies conducted by Saphir *et al.* (1956); Donomae *et al.* (1962), and More and Sommers (1962) have shown, in coronary atherosclerosis, in addition to affection of the main branches, the small arteries also suffer changes displayed by stenosis and even occlusion, which in some cases impairs their anastomotic function. Third, the course passed by the blood before it reaches the reservoir of the affected artery becomes much longer, sometimes nearly doubled, which is naturally accompanied with a slowing of its flow and a drop in pressure. Fourth, the blood flow also slows down because of the plaques, narrowing and roughness in the by-passes, which affects its laminar nature, creates turbulence and, on the whole, leads to a drop in pressure. Fifth, the pressure also drops because the blood passes from a vessel with a wide lumen (main branch) to vessels with narrow lumina (anastomoses) and then again to vessels with wide lumina. According to the laws of hydrodynamics, this leads to a sharp increase in the hydraulic resistance in the region of the anastomosis and simultaneous increase in the pressure gradient, i.e. to considerable drop in pressure at the terminal part of the anastomosis.

Sixth, and the last, with the existence of several parallel anastomoses the loss on friction in them is always greater than in the main vessel, and the hydraulic resistance and pressure gradient increase also with the result that the pressure drops. All this taken together explains the relative importance of anastomoses in compensating for the disturbances in circulation in connection with the affection of any of the main branches of a coronary artery. This is an emergency blood supply adjusted to minimum expenditures or capable of effecting but a slight rise in the minimal level.

All these factors create conditions for a sharp deterioration of the coronary circulation. We therefore hold that, although the development of collaterals through intercoronary anastomoses plays an important role in maintaining coronary circulation, the collaterals are far from always capable of compensating for the decrease in the blood flow through the main coronary trunks.

In stenosing atherosclerosis the requirements of the myocardium in oxygen and nutrients are satisfied within strictly limited boundaries. Even a slight enlargement of the atherosclerotic plaque or an increase in the oxygen requirement of the myocardium may lead to the development of necrosis in the heart muscle.

In severe stenosing atherosclerosis, when the lumen is considerably diminished and the elasticity of many coronary arteries is sharply reduced, conditions are created when even a small increase in the oxygen requirement of the myocardium cannot be produced by an intensified flow of blood through the heart vessels.

Oxygenation of the heart, more than of any other organ, is determined by the amount of the organic blood flow. This is in a large measure due to the fact that even under normal conditions of rest the myocardium extracts about 75 per cent of the oxygen contained in the inflowing blood (Gorlin *et al.*, 1959; McGregor and Palmer, 1963), whereas the other organs, the skeletal muscles in particular, extract only 20-30 per cent (McGregor and Palmer, 1963). That is why, when the oxygen requirement of the myocardium increases, it is mainly satisfied by an increase in the coronary blood flow because the myocardium is almost devoid of the reserve possessed by the other organs.

It is for this reason that the heart, like no other organ, depends on the mechanisms which regulate the coronary blood flow and the ability of the coronary arteries to react adequately to changes in the work loads.

In estimating the functional potentialities of the coronary blood flow it is necessary to consider also the anatomical peculiarities of the cardiac blood channel. It is known that in an anatomical sense the coronary arteries in a healthy heart are not terminal-type arteries. But, if we proceed from the functional potentialities of the heart vessels, we have every reason to regard them as terminal. The intercoronary anastomoses of a healthy heart do not exceed 40 μ in diameter. That is why, when a major branch goes out of order,

these intercoronary anastomoses cannot fully provide for the normal circulation (Nussbaum, 1912; Crainicianu, 1922; Schpalteholz, 1924; Schlesinger, 1938; Blumgart *et al.*, 1950). According to the data of Dorofeeva (1955), worker of the Institute of Cardiology, ligation of the main trunk of a coronary artery results in the flow of only one-fourth of the initial amount of blood to the reservoir of this artery. This explains why in severe stenosing atherosclerosis the least, formerly usual work load, may so easily lead to necrotic changes in the myocardium.

Stenosing atherosclerosis provides conditions for the development of myocardial necrosis even in cases of a very light work load. A disparity between the oxygen requirement of the myocardium and the possibility of providing a sufficient flow of blood may be observed even during slight changes in the coronary arteries, in cases of mild atherosclerosis and sometimes even in the absence of atherosclerotic changes. This is the third possible variant of pathogenic mechanisms of myocardial infarction. In this case the development of myocardial infarction is underlied by functional insufficiency of coronary circulation which may also develop in cases of mild atherosclerosis on a background of considerable work load or under emotional stress. Potain and Huchard pointed out that in these cases a state of relative myocardial ischaemia develops that engenders an attack of pain which, if continued long enough, may lead to irreversible changes. Lang (1936) regarded such ischaemia as one of the most important causes of myocardial dystrophy.

The modern conception of coronary insufficiency is based on the fact that its degree is determined not only by the state of the arterial channel, but also to a considerable degree by the requirement of the heart muscle in blood supply. Clinical observations have been confirmed by a series of experimental studies. Whereas no appreciable necrotic changes were produced by heavy work loads in the myocardium of the animals whose coronary arteries were intact during the first studies (Büchner, 1939), in subsequent studies conducted by S. A. Vinogradov (1957) and Kipshidze (1957), when in addition to an increase in the work load changes were reproduced in the coronary blood flow, it was possible to produce marked necrotic changes in the heart muscle.

S. A. Vinogradov noted that with ligation of a coronary vessel under conditions of an overstrain of the left ventricle owing to the narrowing of the ascending part of the aorta the myocardial necroses were much more spread than in cases of ordinary ligation. They involved not only the parts of the heart muscle supplied by the ligated arteries, but also the adjacent areas.

The closest clinical changes were produced by Kipshidze in experiments on rabbits with experimental cholesterol atherosclerosis in which the vascular lumen was considerably stenosed by the development of lipoidosis. In the myocardium, however, he found only mild dystrophic changes.

In another group of animals who received the same doses of cholesterol, but were simultaneously given systematic work loads (running in a treadmill), not only marked lipoidosis-type changes were observed in the coronary arteries, but also large lesions in the heart muscle in the form of vast multiple necroses.

Thus experimental studies confirm the clinical observations that myocardial infarction may develop in connection with functional insufficiency of coronary circulation. Physical strain may lead to the development of myocardial infarction by conditioning a disparity between the oxygen requirement of the myocardium and the ability of the coronary circulation to provide the necessary amount of oxygen with the blood.

Cases of myocardial infarction in athletes have been described in connection with a considerable work load in the absence of changes in the coronary arteries. According to Myasnikov (1960), such mechanisms produce myocardial infarction in about 16 per cent of cases. He emphasizes the role of physical overstrain and functional insufficiency of coronary circulation in the development of myocardial infarction.

In these cases myocardial infarction is usually observed mainly in young people with moderate atherosclerosis or even in its absence. In rare cases myocardial infarction is connected with coronary thrombosis, but most commonly no thrombi are found in the coronary arteries.

From the point of view of the pathogenic mechanisms of myocardial infarction this is the most complicated group of patients. It is probably very simple to explain the cases of myocardial infarction in which coronary thrombosis is found on a background of moderate atherosclerosis without significant changes in the vascular wall or with unaffected coronary arteries. In the experiment Chazov (1963) managed to produce such changes by combined administration of pituitrin and thrombin to animals with incipient stages of lipoidosis or without any changes in the heart vessels. However, these were rare cases.

It should be emphasized that in such cases the frequency of discovery of thrombi was affected by the anticoagulation reaction that developed in the course of the experiment and was manifest in an increased heparin content and intensified fibrinolytic activity of the blood. In the group of rabbits killed two hours after administration of thrombin and pituitrin we discovered coronary thrombosis in 14 of 21 cases, whereas in animals killed 24 hours after administration of these agents we found it only in two animals. In time the trombus apparently lyses. The result of it is that, while revealing the necrotic changes, the thrombus in the heart vessel may not be found. We think that such a phenomenon is possible not only in animals, but also in man (see above). Smoliyannikov (1958) reports three cases of death from myocardial infarction in connection with coronary thrombosis without marked atherosclerotic changes in the

arteries. Romanov (1963) cites two cases of coronary thrombosis in which a thorough examination failed to find any atherosclerotic changes in the heart vessels.

It should be noted that the appearance of a thrombus with its subsequent lysis can hardly be considered an exhaustive explanation of the development of myocardial infarction in persons without marked atherosclerotic changes or with unaffected coronary vessels. This is probably an extremely rare scheme of the development of myocardial infarction. This is the reason that hypotheses, in many respects still debatable, are employed in explaining the pathogenesis of myocardial infarction in this group of people.

Of considerable interest is the hypothesis voiced by a number of authors on the connection between the development of myocardial infarction and the changes in the sympathico-adrenal system, in particular the proposition on the role of catecholamines in the pathogenesis of coronary insufficiency and myocardial infarction. This trend was elucidated in detail in Raab's studies (1966).

It is known that the sympathico-adrenal system and the products of sympathetic neurosecretion—catecholamines (adrenalin, noradrenalin) play an important role in mobilizing the organism's functions in stress situations, various emotions, etc. This general biological reaction, elaborated during many centuries of the evolution, in the struggle for existence, plays an important role in maintaining the vital activity of various systems and the organism as a whole.

The action of catecholamines manifests itself in activization of the organism's various systems for adapting its existence to new conditions, in mobilization of sources of energy in increasing the consumption of energy substrates and in an increased consumption of oxygen by the tissues connected with it. Under the influence of catecholamines the level of physiological activity of the cardiovascular system aimed at providing the function of the muscles rises rapidly, i.e. the pulmonary vessels and bronchioles dilate for better oxygenation of the blood, the requirement of oxygen and its consumption by the myocardium sharply increase, coronary vessels dilate, coronary blood flow intensifies, the force of cardiac contractions and ejection increases, etc.

As Chazov's studies conducted jointly with Meerson (1960) have shown, the content of catecholamines in the myocardium determines the development of compensatory hyperfunction and then hypertrophy of the myocardium.

Usually the situations in which the sympathico-adrenal system and catecholamines are mobilized last but a short time and when they terminate not only the increased secretion of catecholamines ceases, but even the hormones secreted in a large amount into the blood become inactivated within a few minutes. According to Shtraub (1963), almost 80 per cent of catecholamines are inactivated during a single passage of the blood through the liver.

The response reactions to stresses elaborated in the animals in the course of evolution precede muscular tension and a sharp increase in muscular work. The intensified secretion of catecholamines is accompanied with a subsequent muscular reaction and rapid utilization of catecholamines.

In man the stresses are most commonly not accompanied with muscular work, but the increased catecholamine secretion consolidated in the course of evolution persists. The result of it is that under such conditions the content of catecholamines increases and the work of the heart is reorganized on a new energy and functional level, which, however, is not followed by an increase in the work of the skeletal muscles. The studies of many authors have demonstrated the injurious effect of catecholamines on the myocardium. As far back as 1907 Josue observed the development of degenerative and local necrotic changes in the myocardium of animals given large doses of adrenalin. Subsequently many investigators observed an appearance of necrotic changes in the myocardium under the influence of an excess of catecholamines (Gollwitzer-Meier *et al.*, 1936; Cannon, 1939; Danilova, 1961; Amelin *et al.*, 1963; Raab *et al.*, 1964; Probatova, 1965; Pevzner, 1969).

The mechanism of the toxic, necrotic effect of excessively secreted catecholamines is still undetermined. Some authors associate the appearance of necrotic changes in the myocardium under the influence of catecholamines with myocardial hypoxia due to the disturbance in the balance between the oxygen requirement and oxygen supply through the coronary arteries. Under these conditions coronary arteries, even dilated to the limit, cannot satisfy sharply increased oxygen requirement of the myocardium.

In Raiskina's opinion (1967), adrenalin and noradrenalin sharply reduce the ability of the myocardial cells to assimilate oxygen, which is the reason for the development of histotoxic hypoxia of the myocardium. Certain authors (Eckstein *et al.*, 1951; Katz *et al.*, 1956; Whalen, 1957; Berne, 1958; Marchetti *et al.*, 1963) hold that under the action of catecholamines the consumption of oxygen by the myocardium exceeds its requirement conditioned by its actual work, i.e. the catecholamines squander, as it were, the oxygen.

The controversy of a number of propositions on the effect catecholamines produce on the myocardium is confirmed by extant views, for example, of Gerola *et al.* (1954); Krasnow *et al.* (1964), and Klocke *et al.* (1965), who hold that catecholamines have no direct metabolic effect on the heart muscle and that the increased oxygen requirement is conditioned by the changes in haemodynamics under their influence.

Despite the debatable nature of the question concerning the mechanisms of the development of necroses in the myocardium under the influence of catecholamines the very fact of the appearance of necrotic changes cannot be doubted. The only question that arises

is: why do emotional states and stresses favour the appearance of necroses in the myocardium in some cases, while in other cases necroses do not develop? The soundest opinion is probably that of some authors, for example, Levi (1966) that there is an individual reactivity of the sympathico-adrenal system with inadequate secretion of catecholamines in response to emotional influences. In such cases myocardial ischaemia may develop even with relatively slight anatomical changes in the heart vessels. Another variant is also possible, when in more marked changes in the coronary arteries a moderate secretion of catecholamines into the blood may cause injury to the myocardium.

From the point of view of individual peculiarities of catecholamine secretion attempts are even made to distinguish people with a marked catecholamine reaction to external influences. Thus Mason *et al.* (1961); Raab *et al.* (1964), and Levi (1966) have shown that in physically inactive brain workers the sympathico-adrenal system predominates, i.e. there is an increased secretion of catecholamines in response to various external influences. Rosenman *et al.* (1966) noted a similar reactivity in emotionally labile people.

It is known that nicotine stimulates the sympathetic system and creates conditions for intensive catecholamine secretion (Regan *et al.*, 1961; Bellet, 1966, and Doyle, 1966). As observations of Selye (1952) and Raab (1966) show, the effect of physiological doses of catecholamines in cases of emotional stress considerably increases and becomes injurious because it adds to the effect of corticosteroids. Raab found that administration to rats of 200 γ of adrenalin per 100 g of body weight causes no change in the myocardium, but simultaneous administration of 250 γ of fluorocortisone is followed by the formation of micronecroses in the hearts of the experimental animals.

An unfavourable effect is also produced by a shortage of potassium ions in the myocardium. According to Darrow and Miller (1942); Nickerson *et al.* (1961), and Müller (1962), under the effect of excessive catecholamines the myocardium loses potassium, which renders it extraordinarily sensitive to hypoxia. On the other hand, the very damage that results to the myocardium also leads to a loss of potassium by it (Prinzmetal *et al.*, 1961; Salmanovich, 1961; Andreichev, 1963; Raiskina *et al.*, 1963, etc.). The result is a vicious circle. In discussing the questions of the influence of catecholamines on the myocardium it should be pointed out that, according to several authors, the neurogenic influence on the myocardium is also accompanied with a change in their content in the heart muscle. For example, according to Menshikov and Usvatova (1963) and Shkhvatsabaya (1965), during stimulation of the higher parts of the nervous system of rabbits by introduction of air into the ventricles of their brains the resultant myocardial necroses were accompanied with a change in the content of catecholamines. A considerable increase in the content of adrenalin and to a lesser degree of noradrenalin and also

marked decrease in the concentration of potassium and an increase in the content of sodium were observed in the myocardium. Thus the neurogenic influence on the coronary blood flow may be mediated through a change in the content of catecholamines.

We are not inclined to regard necroses arising in connection with the influence of catecholamines as necroses of noncoronary origin. We hold that the coronary factor plays an important role in the appearance of necrotic changes in the myocardium also under the action of catecholamines. The functional disparity between the oxygen consumption by the myocardium and the supply of oxygen by the coronary vessels is undoubtedly due to the state of the coronary circulation. Thus under the action of catecholamines necroses are essentially of coronary origin.

What is the mechanism of the development of necroses in the myocardium in cases of disturbances in neuroregulation under neurogenic stimulation? Is it a result of a spasm of the coronary vessels or is a certain role played by a change in myocardial metabolism, the metabolism of hormones, which may be effected by stimulation of both the peripheral and central nervous systems?

The role played by sympathico-adrenal effects in connection with neurogenic stimulation and by catecholamines in the development of acute coronary failure is indirectly confirmed by the fact that the blocking of these effects with hexamethonium or other substances (ganglioplegics, atropine) prevents ischaemic changes in the electrocardiogram and changes in the myocardium (Kaverina, 1958; Kisin and Sinitsyn, 1963, and Shkhvatsabaya, 1965). At present extensive clinical and experimental material has been accumulated which indicates the importance of the neurogenic factor in the development of acute coronary failure and necrotic changes in the myocardium. Ischaemic-type changes in the electrocardiogram and, in a number of cases, the appearance of myocardial necroses have been found in various affections of the brain (Koreisha, 1939; Kandel, 1950; Vinogradova, 1957; Schmidt *et al.*, 1963). It should be emphasized that in these cases there are circulatory disturbances of a functional and organic character: contraction or paretic dilatation of intramural arteries, diapedetic haemorrhages, haemorrhages under the endocardium, and micronecroses of muscle fibres (Desyatov, 1952; Schmidt *et al.*, 1963; Vikhert, 1969, and others).

Similar changes were also found in experiments with stimulation of various parts of the central nervous system (Vinogradova, 1957; Melville, 1964; Shkhvatsabaya, 1965, and others). The effect of this stimulation manifested in necrotic changes in the myocardium may undoubtedly be connected with metabolic disturbances in the myocardium and with changes in the content of hormones, in particular of catecholamines. However, the hypothesis of the importance of metabolic changes in the pathogenesis of neurogenic affections of the myocardium gives rise to objections in connection with the existing views on the nervous and neurohumoral influen-

ces on the tonus of the coronary vessels and in virtue of this on the coronary circulation. Myasnikov pointed out: 'Disorders of coronary circulation are often, or to a great extent, connected with a functional narrowing of the coronary arteries underlied by an increase in the contractile or tonic properties of their walls. These contractions set in acutely and for a short period and are therefore called spasms'. Considerable importance to spasm of coronary arteries, as one of the important links in the pathogenesis of myocardial infarction, is also attached by clinicians and pathologists (Gilbert, Lang, Leary, Lukomsky, Myasnikov, Tareev, White, and others).

Kaverina, Trubetskoy, and Shkhvatsabaya (on the basis of experimental studies), and Abrikosov, Avdeev, Davydovsky, Smoliyannikov, Strukov (on the basis of certain pathological data) point out the importance of spasm in the development of angina pectoris and myocardial infarction. Naturally, the hypothesis of the importance of coronary spasm in the pathogenesis of infarction finds confirmation, primarily in clinical observations. The main proof is the reference to nervous tension and nervous shock which precede the appearance of angina pectoris or myocardial infarction.

From the clinical point of view the appearance of spasm in connection with reflex influences serves as proof of its importance in coronary disorders. The paroxysmal course of angina pectoris with subsequent development of myocardial infarction creates an impression that vascular spasm underlies the disease. The possibility of neurogenic spasm was demonstrated on healthy animals in a series of experimental studies (Kaverina, 1959; Trubetskoy, 1964, and Shkhvatsabaya, 1965). However, spasm of coronary arteries is still a very moot point.

In experiments on healthy animals (rabbits) with simultaneous administration of pituitrin, a substance which leads to spasm of the coronary arteries, and thrombin, one of the end enzymes in the chain of blood coagulation, we managed to produce coronary thrombosis in a small percentage of cases, and small myocardial necroses in half the cases.

Despite the vast experience of clinicians and seemingly demonstrative experimental studies, and despite the opinion of a large number of pathologists the importance of vascular spasm in the development of myocardial infarction is not clear as yet. For example, a number of studies (Boyer and Green, 1941; Eckenhoff and Hafkenschiel, 1947, and Kisin and Zubovskaya, 1964) doubt one of the important arguments used in favour of vascular spasm, namely, the vasodilatative action of nitrates. The authors of these studies assert that nitrates (nitroglycerin) possess no coronary vasodilatative action. The analgesic effect of nitroglycerin during an attack of angina pectoris is connected with a decrease in energy processes in the myocardium (Hunter *et al.*, 1953; Gorlin *et al.*, 1959; Rowe *et al.*, 1961, and Bender *et al.*, 1963) and a corresponding decrease in its oxygen consumption.

It should be emphasized, however, that the opinion on vasodilatative effect of nitroglycerin on coronary arteries has of late been confirmed by coronary angiography which showed its dilatative effect. In an experimental study on dogs Mazaev, worker of the Institute of Cardiology,. specially investigated the effect of nitroglycerin by the method of coronary angiography and clearly showed that noradrenalin dilatates mainly the major coronary arteries, while nitroglycerin produces effect both on the major and minor arteries.

Why then does the proposition on the importance of spasm in the development of myocardial infarction still remain a hypothesis? The doubt is associated mainly with the fact that it is difficult to believe that a spasm may arise in atherosclerotically changed coronary arteries with rigidly thickened walls. The second objection against the importance of spasm in the development of myocardial infarction is that myocardial infarction very seldom occurs in the right ventricle and develops there solely in cases of severest stenosing atherosclerosis of the right and one of the branches of the left coronary arteries. The question that naturally comes up is: why does spasm of the coronary arteries suffice for myocardial infarction of the left ventricle, whereas infarction of the right ventricle necessarily requires considerable atherosclerotic changes in the vessels?

Speaking of the importance of coronary spasm in the development of myocardial infarction it should be remembered that for the development of an infarction the spasm with complete cessation of coronary circulation or its sharp arrest must last at least 30 minutes because ischaemia of a shorter duration does not result in myocardial necrosis. The question of the importance and role of coronary spasm in the pathogenesis of myocardial infarction undoubtedly requires further study.

The development of myocardial infarction with marked atherosclerosis and the absence of thrombosis suggests a coincidence of certain unfavourable factors which condition the disturbance in coronary circulation.

In this case the following variant is possible. First, the presence of atherosclerosis. Unfortunately, the concept of 'feebly marked atherosclerosis' is very subjective and has no precise definition. In evaluating the possible pathogenic mechanisms we proceeded from the proposition that it is a single plaque which occupies not more than half the circumference of one of the main coronary arteries and does not stenose its lumen. Second, weak development of anastomoses because of the slight stenosis of the coronary arteries (Smoliyannikov and Naddachina, 1963) owing to which they are of a very little functional importance. In cases of even a single plaque the possibility for dilatation of the coronary arteries and thereby for an increase in coronary circulation is relatively limited. For example, with a 50 per cent increase in the radius of the vessel its sectional area and, consequently, its blood flow increase 125 per

cent. These correlations are disturbed even in the presence of a single atherosclerotic plaque and the area of the lumen increases only 40-50 per cent (Fig. 36), whereas during moderate muscular work the coronary blood flow must increase 200 per cent and during hard work 300 per cent. It should be remembered that the transition from a state of rest to physical work is accompanied by a rapid change in cardiac activity, i.e. during the first minute the ventri-

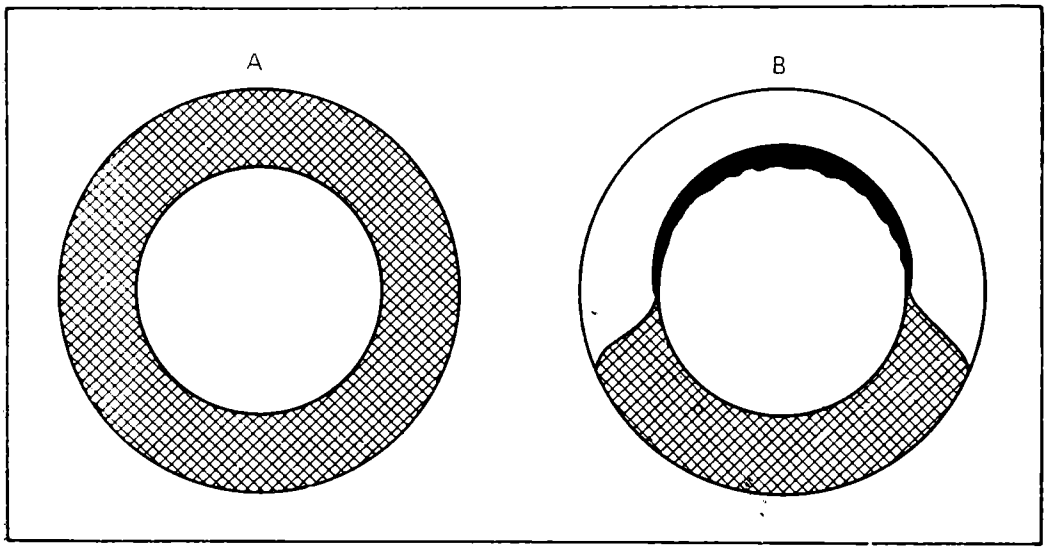

Fig. 36. Influence of the atherosclerotic plaque on the capacity of the coronary artery to enlarge the lumen. Upon a 50 per cent increase in the radius the area in an unaffected vessel increases 125 per cent (*A*). In the presence of atherosclerotic plaque the area increases only 40-50 per cent (*B*) because the plaque cannot expand (the shading shows the increase in the area of the vessel of its expansion and a 50 per cent increase in the radius)

cular ejection increases 100 per cent and under a heavy work load even more (Andersen, 1968).

Under unfavourable circumstances, for example, in case of need for a sharp physical strain in a person leading a sedentary life and smoking a good deal such a work load on a background of neuropsychic overstrain accompanied with a secretion of a large amount of catecholamines gives rise to a combination of unfavourable factors which, in the absence of adequate collateral blood circulation, create conditions for myocardial ischaemia.

For example, consumption of alcohol the day before or the same day, the impoverishment of the myocardium in potassium ions under the influence of intensified secretion of corticoids in connection with stress, etc. may play the role of unfavourable factors. An objection may be raised that such a combination occurs not frequently, but myocardial infarction with little changes in the coronary arteries is also an unusual occurrence and its rareness is due to the necessity for a simultaneous combination of a number of unfavourable

factors. It is perfectly clear that in cases of usual reactivity and unaffected vessels neither great physical strain nor strong emotional influences lead to myocardial infarction.

On the grounds of what was stated above it may be assumed that the aetiological basis for myocardial infarction is coronary atherosclerosis on the background of which several anatomical and functional factors contribute to the development of the infarction. A solution of the problem of atherosclerosis, coronary atherosclerosis in particular, will actually lead to the solution of the problem of myocardial infarction and a sharp decrease in its incidence. This is evidenced by the infrequency of myocardial infarction in countries where the incidence of atherosclerosis is lower, e.g. in Japan. The significance of atherosclerosis is also evidenced by the difference in the incidence of myocardial infarction in men and women, which parallels that of the markedness of coronary atherosclerosis at different age periods. In women the affection of coronary arteries 'lags' 10-15 years behind that in men, and myocardial infarction correspondingly occurs 10-15 years later. Only after 70 years of age, when coronary atherosclerosis reaches about the same level in both sexes, does the incidence of myocardial infarction even up (Vikhert *et al.*; Vikhert and Matova).

Experimental data also indicate the significance of atherosclerosis as the basis for the development of myocardial infarction, when the changes very similar to myocardial infarction were produced only by combining atherosclerotic changes in the vessels with additional pathogenic influences. Evidently, influences on the various aspects of pathogenesis of myocardial infarction and elimination of a number of unfavourable pathogenic factors from the life of modern man constitute one of the most important tasks in the control of this disease.

3

EPIDEMIOLOGY OF ISCHAEMIC HEART DISEASE

In the last twenty or thirty years epidemiological research in chronic non-infectious diseases has been widely conducted in many countries. The most complete epidemiological information has been obtained on various manifestations of the ischaemic heart disease (IHD)[1]. The primary reason for it is that in the modern world this disease has become notorious because of its wide distribution and as one of the main causes of sudden death, loss of health and working capacity, as well as disability of a large contingent of people, especially men, often in the prime of life.

Today the correct use of the term 'epidemiological research' in regard to various manifestations of IHD, whether angina pectoris, myocardial infarction or sudden death of cardiac aetiology, is no longer doubted by anybody.

The following figure offers an idea of the enormity of the epidemic: according to official data (President's commission on Heart Disease, Cancer and Stroke. Report to the President, 1964, p. 2-7), 546 813 persons died of ischaemic heart disease in the USA in 1963. It is perfectly clear that this can be regarded precisely as an epidemic, even if extended in time, since not every epidemic of an infectious disease reaped so abundant a harvest in the past. If we add to this the number of people who contracted the disease, were disabled and had to change their occupation, etc. the picture will appear even more dismal. According to the US Board of Health,

[1] Ischaemic heart disease is manifest as angina pectoris, sudden death, myocardial infarction and atherosclerotic cardiosclerosis. The data on epidemiology of IHD pertain to the two last manifestations and may, on the whole, be used in judging of epidemiology of myocardial infarction.

in 1960-1962 there were 3 100 000 registered and at least 2 400 000 unregistered IHD cases in the USA.

Epidemiological research is aimed, first, to study the distribution of IHD among various age, occupational and national groups of people and second, to elucidate the role which factors of the external environment play in the development of IHD: climate, dietary features, various habits (smoking, alcohol consumption), living and working conditions, occupation and their emotional aspects.

The rules of the epidemiological research in chronic non-infectious diseases must naturally differ from the canons generally accepted in epidemiological research in virtue of the complexity of their aetiology and pathogenesis. Its importance lies in the fact that it makes it possible, on the basis of a number of signs, to predict the probability of IHD development among the investigated group of people over a certain period of time. This cannot be achieved by any other method of research in chronic diseases.

The chances to predict the probability and incidence of IHD were formulated as a concept of so-called risk factors which are certain deviations from the biochemical or clinical indices, e.g. that of the blood cholesterol level, electrocardiogram, elevated arterial pressure, some habits, particularly excessive smoking or eating with a rapid increase in body weight, or diminished physical activity. The presence of one or simultaneously several risk factors over a certain period of time is an indication of an increased probability of the development of symptoms of a vascular catastrophe.

An important role in elucidating the importance of the risk factors was played by epidemiological research in Framingham and Tecumseh (USA). On the basis of observing the population of these towns over a long period of time Epstein (1965) established a possibility of predicting by various signs the number of people who would develop IHD. He calculated, for example, that, if 156 men out of 1000 have hypercholesterolaemia above 260 mg per cent in the beginning of the observation decade, 32 of them will develop one of the manifestations of IHD—myocardial infarction, angina pectoris, chronic heart failure of coronary genesis, or some of them will die suddenly during the observation period, while the other 124 men will stay practically well despite having one of the risk factors (hypercholesterolaemia). It follows that the 'predictive' value of the risk factor is 21 per cent. However, a combination of several risk factors, e.g. hypercholesterolaemia, hypertension, chain-smoking and excess weight, increases the probability of the development of IHD manifestations to 44 per cent, i.e. nearly half the number of people with four risk factors will develop IHD in the course of ten years (Epstein). But, other conditions being equal, it is impossible to predict precisely who of the investigated group of people will develop the disease. Elucidation of the role played by the risk factors offers extensive opportunities for carrying out prophylactic measures, namely, cessation of smoking, change in diet to reduce

the level of cholesterol and the boby weight, elimination or abatement of hypertension, etc. Thus epidemiological studies merge with preventive medicine in a broad sense of the term. According to Paul (1966), 'preventive medicine utilizes epidemiology'.

In the Soviet Union epidemiological studies of IHD and hypertensive vascular disease began about fourteen years ago on the initiative of Academician A. L. Myasnikov (USSR Academy of Medical Sciences) and are now being conducted very widely. In addition to examining certain groups of people studies are also made of the coronary arteries obtained in autopsies in various cities of the country which are carried out in close contact with the Department of Cardiovascular Diseases of the WHO. A common method makes it possible to obtain comparable results not only in one country. but also on an international scale.

Below we shall cite some data furnished by the studies of the IHD epidemiology, in particular its distribution and the role played by various risk factors.

Distribution of Ischaemic Heart Disease

It is quite difficult to form an opinion about the distribution of IHD among the people of various countries because in most cases it is not so easy to compare the data cited in literature owing to the differences in the methods of examination, the age and occupational composition of the investigated groups of people, the criteria used by the authors to confirm IHD diagnosis, the system of recording the disease, etc.

Summary data on mortality from atherosclerotic heart diseases[1] are systematically published by the WHO. Table 4 which we compiled on the basis of WHO random information shows data pertaining mainly to European countries. We have listed the countries roughly in the order of their mortality incidence and took only males and separate age groups. According to the Table, mortality from atherosclerotic heart diseases has persisted on a high level in a number of countries all through the years. They include Scotland, Northern Ireland and England, Finland, the GDR, FRG, Denmark and Austria. On the other hand, in Poland, Yugoslavia, Bulgaria, Greece, Portugal and France mortality from atherosclerotic heart diseases has persisted no less steadily on a low level, 66.7-75 per cent of that mentioned for the foregoing countries. Outside Europe the highest mortality is among the white and non-white population of the USA (according to the data of 1958, it was 1157 and 1032 per 100 000 population among males 60-64 years of age, respectively). At the same time mortality from these diseases is very low in Japan.

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[1] The term used by the WHO is collective and comprises myocardial infarction, postinfarctional cardiosclerosis, chronic coronary insufficiency, etc.

Table 4. Mortality from Atherosclerotic and Degenerative Heart Diseases

Country	1958	1964		1965
	50-54 years	60-64 years	45-64 years	55-64 years
Scotland	343	1080	644	968
Finland	405	1029	708	1037
Northern Ireland	392	974	540	856
England	272	774	458	717
GDR	264	676	—	—
Denmark	184	603	364	586
Austria	172	581	480	477
FRG	194	574	367	549
Sweden	152	568	297	489
Norway	182	558	334	583
Switzerland	157	509	250	389
Netherlands	153	476	313	385
Italy	152	460	248	503
Hungary	151	439	292	386
Czechoslovakia	—	—	293	453
Belgium	—	—	270	418
Poland	—	—	184	281
Yugoslavia	—	—	176	267
Bulgaria	—	—	103	176
Greece	—	—	105	161
France	—	—	138	206
Portugal	80	308	145	256
USA white	467	1157	—	—
USA non-white	441	1032		
Japan	70	187	—	—

Interesting data on increased mortality from cardiovascular diseases in the eastern sector of Berlin are cited by Scheidler (1963). In 1925 it amounted to 19.1 per 10 000 population, in 1932 22.9, in 1953 35.8, in 1959 52.4 and in 1961 57.3, i.e. in 35 years it increased three-fold. It should be remembered that in most of the cases death was caused by various IHD manifestations. Analogous phenomena were noted by Björck in Malmö (Sweden). From 1924 to 1942 mortality from IHD (especially from myocardial infarction) increased several times both among males and females. It continued to increase steadily during the subsequent years amounting to 1.08 for men and 0.36 for women per 1000 population in 1952, 1.6 and 0.52 in 1955, and 2.78 and 1.05 in 1959, respectively, i.e. having nearly tripled. According to Acheson (1961) mortality from IHD among males over 40 years of age amounted to 964 per 10 000 in the USA in 1954. Groom (1961) cited even higher figures: mortality amounted to 704.7 for only one decade of life (males 50-59 years of age). Analogous data may also be found in other sources.

It is interesting to compare the findings of some investigations specially conducted in different countries. In Fukuoka (Japan) a

study was carried out in which all people died in the city were subjected to an autopsy. In Malmö (Sweden), where there is only one hospital, 80-100 per cent of the deceased were also subjected to autopsies (including coroner's inquests). The data on the causes of death in Fukuoka were published by Sumigoshi *et al.* in 1965, and those in Malmö by Sternby in 1968.

In Fukuoka a fresh infarction was found in men over 40 years of age in 0.31 per cent and scars after a survived infarction in 2 per cent of the autopsies. In Malmö coronary disease was the cause of death in 30.2 per cent of the men over 40 years of age. These data indicate that in Malmö coronary death among males occurs 10 times

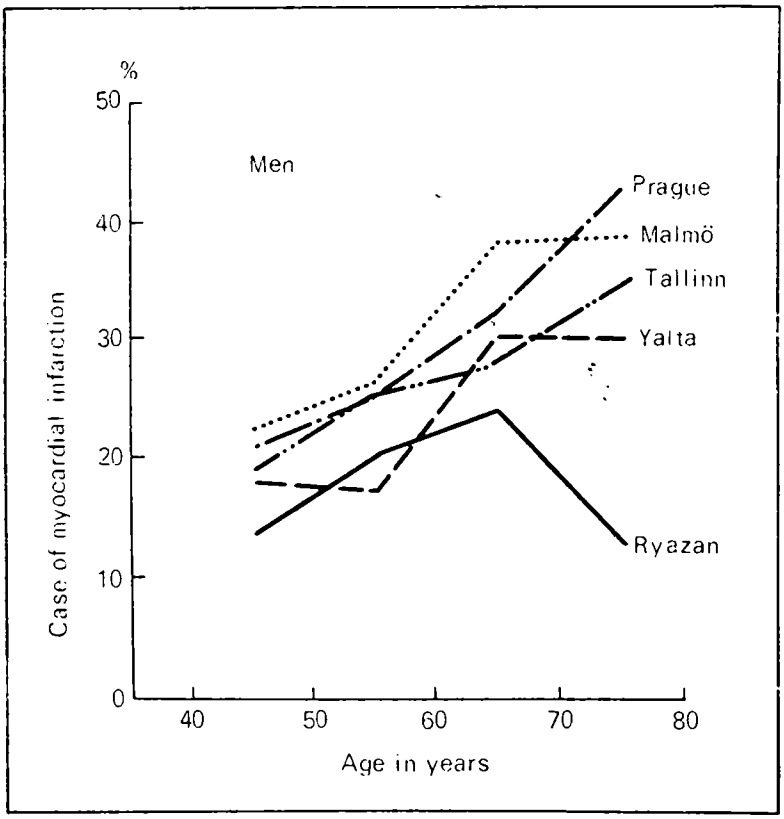

Fig. 37. Incidence of myocardial infarctions in per cent to males who died in various cities

as often as in Fukuoka. It is also noteworthy that in Malmö the highest incidence of coronary death in females occurs about ten years as compared to males: at 50-59 years of age it constitutes 26.6 per cent of all fatal cases of males and only 6.8 per cent of females; at 60-69 years of age it is 36 and 23 per cent, respectively. Only after 70 years of age do the figures reach the same level in both sexes—about 32-34 per cent.

Joint studies conducted in accordance with the WHO programme in Prague (CSSR), Malmö (Sweden), Tallinn, Yalta and Ryazan

(USSR) in 1964-1968 with compulsory autopsies of at least 80 per cent of fatal cases also showed considerable differences in the incidence of myocardial infarction in these cities. The highest incidence was observed in Prague and Malmö, then in Tallinn and Yalta, whereas in Ryazan myocardial infarction figured as a cause of death less frequently in all the age groups of both men and women (Figs. 37 and 38).

It is noteworthy that there was a correlation between the incidence of infarctions and that of coronary stenosis; stenosing coronary atherosclerósis was observed the least frequently among the

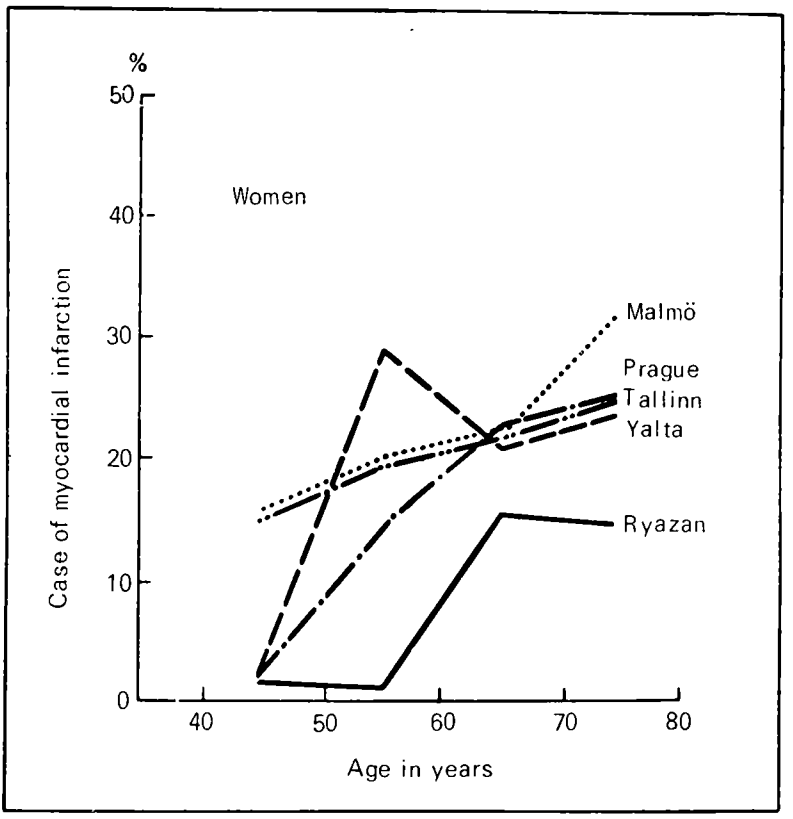

Fig. 38. Incidence of myocardial infarctions in per cent to females who died in various cities

people of Ryazan and the most commonly among those of Prague and Malmö (Fig. 39).

Literature contains data on IHD incidence; in England it was found in 9.3 per cent of males 60-64 years of age (Brown *et al.*, 1957), according to Higgins *et al.* (1963), in 24.1 per cent of rural population (55-64-old males) and 20.2 per cent of miners, according to other authors it was found in 37 per cent of males 65-69 years of age (Acheson, 1961) and in Tecumseh (USA) in 18 per cent of males 60-69 years of age (Epstein, 1967), Fodor *et al.* (1968) found a very high

incidence of IHD in their epidemiological study of 50-54-year-old males in one of Prague's boroughs (Prague II): of the 443 men chosen at random 21.42 per cent had angina pectoris of various severity, while 10.6% per cent had survived myocardial infarction, i.e. more than 30 per cent had various manifestations of IHD. It is interesting that the disease had been diagnosed and recorded before the study only in 11.3 per cent of patients and in two-thirds it was revealed during the study. It is easy to notice considerable disparity in the data of the various authors, which in all likelihood is largely

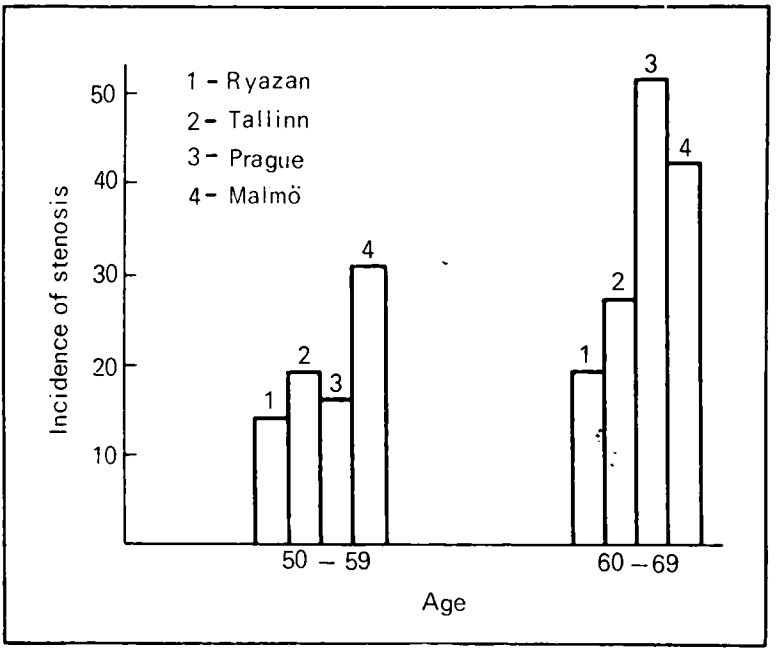

Fig. 39. Incidence of stenosis of the descending branch of the left coronary artery in males

determined by the differences in methods, absence of a common terminology, diagnostic criteria and by discrepancies in interpreting the results.

Many studies in the epidemiology of IHD have of late been conducted in various Soviet cities. Their advantage lies in the fact that they were coordinated and directed by the Institute of Cardiology (USSR Academy of Medical Sciences). This ensured a relatively common method of investigation and made it possible to obtain comparable results.

According to Sedov (1969), in Irkutsk there was the following incidence of heart disease in persons over 30 years of age: angina of effort 27.5, myocardial infarction 0.65 and atherosclerotic cardiosclerosis 135 per 1000 population, and mortality from myocardial infarction 31 per 100 000 population.

In Sverdlovsk, according to Barats (1964), coronary atherosclerosis was found in 3.41 per cent of mental workers and in 1.23 per

cent of manual workers (indices standardized by age). A rather higher IHD incidence among males over 40 years of age in Ufa is cited by Mingazitdinova (1969), namely, 3.7 per cent among manual workers, 6.9 per cent among engineers, technicians and administrative workers, and 9.1 per cent among scientific workers. In Andizhan coronary atherosclerosis was observed in 5.8 per cent of men between 30 and 59 years of age, the incidence amounting to 3.2 per cent among the native population and 8.8 per cent among the non-natives. The highest incidence of the disease occurs at 50-59 years of age and amounts to 11.4 per cent among both groups of the population (Konstantinov, 1969). In Novokuznetsk Goldberg (1964) and his associates found the incidence of IHD among men 50-69 years of age to range from 17.9 to 31.3 per cent, depending on the level of blood pressure (see below).

Interesting (but requiring verification) indices of incidence of myocardial infarction in Kiev are mentioned by Sherstnev (1969). In 1960 this index amounted to 6.6, in 1962 to 8, and in 1966 to 13.9, i.e. it doubled in six years while total mortality decreased from 43.4 in 1960 to 30.8 in 1966. According to the Kolomna angio-radiological centre, IHD was observed in 15.6 per cent of men 50-54 years of age, whereas in Ryazan, where men are examined at 55-64 years of age in keeping with the WHO programme, IHD was found in 10.7 percent.

In Moscow examinations of groups of men 50-59 years of age living in Bauman district and chosen at random revealed various manifestations of IHD in 19.5 per cent, including myocardial infarction in 7.4 per cent (Metelitsa *et al.*, 1970).

In the Soviet Union, according to epidemiological data, the incidence of myocardial infarction is the highest in Moscow. In one of the city districts Kalinina and Bogoslovsky (1964) found the incidence among people over 40 years of age to be 8.56 for men and 2.8 for women per 1000 of population. Examinations in other cities revealed much lower figures. In Kiev (in 1962) they were 3.94 per cent for men and 1.22 per cent for women (Krister *et al.*, 1964). The lowest incidence was noted in Krasnoyarsk (Opaleva-Stegantseva *et al.*, 1965), 2.5 per cent among men and 1.9 per cent among women. From the above it follows that in Moscow the incidence is 2.5-3 times as high as in other Soviet cities and that in other cities the incidence among men is but slightly higher than that among women living in Moscow.

In conclusion we shall cite some data on the markedness of coronary atherosclerosis in a number of countries and cities. We consider it necessary because the development of IHD is associated with coronary atherosclerosis. The studies were conducted in accordance with the WHO programme. The three main coronary arteries were studied in all the cases. The area involved in the atherosclerotic changes or their different types (fibrous plaques, complicated affections, calcinosis) was determined and stenosis of more than

50 per cent of the vascular lumen was taken into account. The resultant data were processed statistically.

Atherosclerotic changes in the coronary vessels are man's fate already at an early age. If fibrous plaques are to be regarded as their initial manifestations, it turns out (Table 5), that 8 per cent of males suffer from atherosclerosis of the abdominal aorta at 10-19 years of age, and 24 per cent from that of the descending branch of the left coronary artery. At 20-29 years these figures rise to 20 and 48.1 per cent, respectively (in women they are somewhat lower).

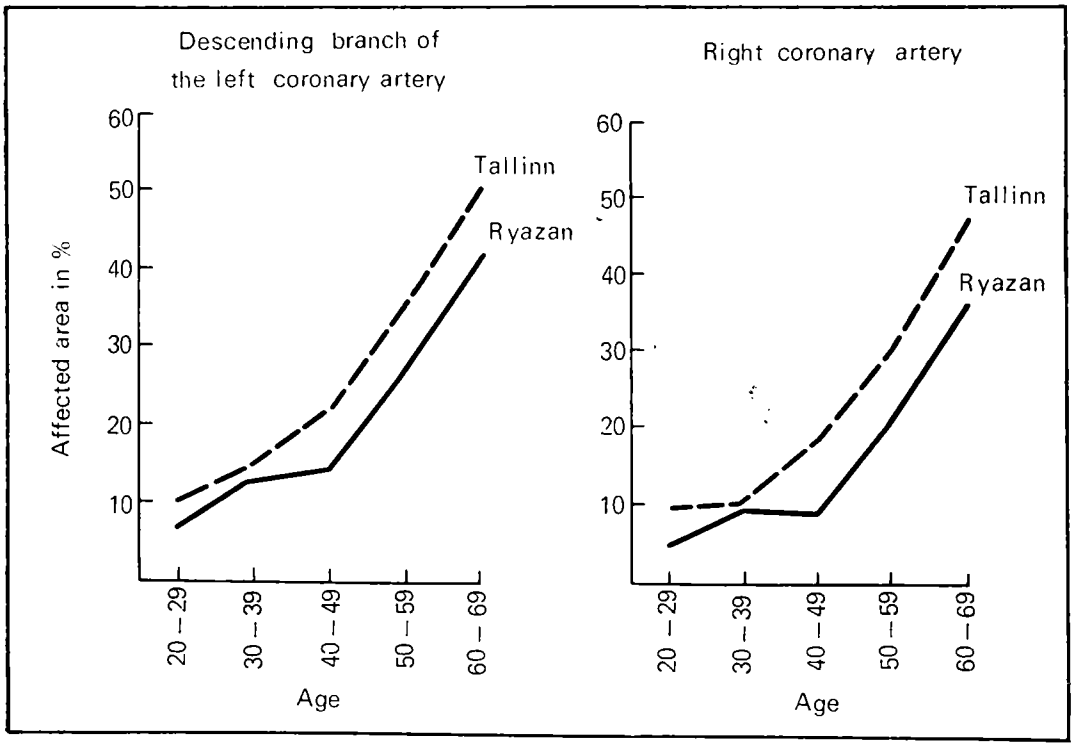

Fig. 40. Total area of atherosclerotic changes in the descending branch of the left coronary artery and the right coronary artery in percentage to area of the vessel in females in Tallinn and Ryazan

As Table 5 shows, the incidence increases with age, but the disease does not necessarily occur in older groups since even at 60-69 years of age 2.8 per cent of men and 9.9 per cent of women have no coronary atherosclerosis.

Thus, although atherosclerosis is a very frequent disease, it cannot be considered a necessary part of age.

In urban population atherosclerosis of the coronary arteries may be of various severity. This is clearly seen on the example of Tallinn and Ryazan. Both cities have about the same population (300 000-350 000) and equally developed industry. However, the affection of coronary arteries is more severe (statistically reliably) in Tallinn,

Table 5. Atherosclerosis in Practically Healthy People of Various Age

	Percentage of healthy people with atherosclerotic changes at 10-29 years of age				Percentage of healthy people without atherosclerosis at 50-69 years of age			
	10-19 years		20-29 years		50-69 years		60-69 years	
	men	women	men	women	men	women	men	women
Abdominal aorta	8.0(41)	12.5(32)	20.0(330)	18.4(130)	7.3(233)	9.4(96)	2.0(149)	0.0(82)
Descending branch of left coronary artery	24.0(41)	6.3(32)	48.1(316)	30.3(122)	7.3(232)	19.8(91)	2.8(143)	9.9(81)

Note: In parentheses is the number of cases.

both in men and women (Fig. 40). Moreover, the severity of stenosing forms, especially among older people, is also higher (Fig. 41). Correspondingly, mortality from complications of atherosclerosis and hypertension (mainly from myocardial infarction) is lower in Ryazan than in Tallinn (Fig. 42)[1]. It is not clear why Ryazan is in such a favourable position and why myocardial infarction as the cause of death occurs among its inhabitants 33.4-66.7 per cent less frequently. Ryazan does not particularly differ from any other city.

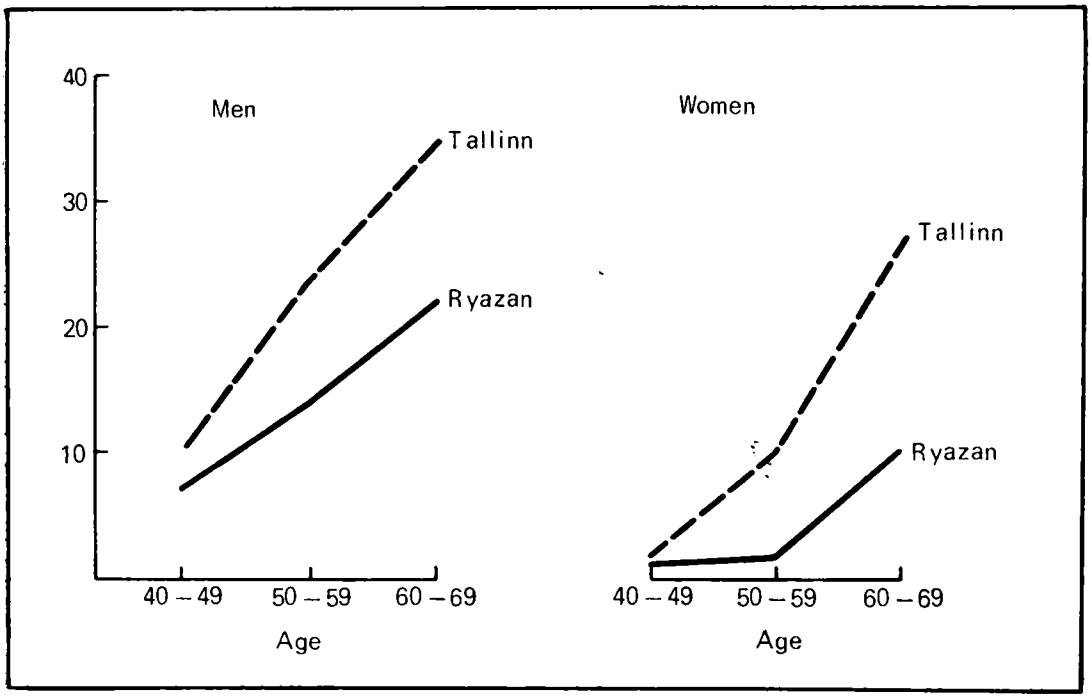

Fig. 41. Incidence of coronary stenosis (in per cent to the number of observations) in the inhabitants of Tallinn and Ryazan

It is only 180 km from Moscow, but in Muscovites atherosclerosis, including that of the coronary arteries, develops earlier and more frequently and is more severe than in the population of Ryazan.

As we have already stated, Tallinn and Ryazan are cities with a developed industry. A large part of their adult population consists of industrial workers. For comparison we can take a city with other climatic conditions and a weakly developed industry, e.g. Yalta. It appears that both cities have the same incidence of stenosing atherosclerosis of the coronary arteries (Fig. 43) and myocardial infarction occurs not less frequently and in some age groups even somewhat more frequently in Yalta (Fig. 44). Thus favourable climatic conditions do not prevent the development of coronary atherosclerosis.

[1] Comparative data on these cities, Prague and Malmö were cited above.

Of some interest is also the question of the markedness of coronary atherosclerosis in the non-European part of the Soviet Union, i.e. in Central Asia and Siberia. To elucidate this question, a study was made of atherocalcinosis since there is an interdependence between the markedness and severity of atherosclerosis and the deposition of calcium salts in the arteries. Atherocalcinosis was studied by the roentgenographic method in four geographic zones of the Soviet Union, the Baltic zone (Riga and Tallinn), Central Asia (Frunze, Ashkhabad), Kharkov and Irkutsk. For the most complete discovery of calcinosis 6500 aortas and their corresponding coronary vessels were studied by means of photography on a roentgen film in mild rays (30 mA current, 30 kW, at a distance of 70 cm from the tube).

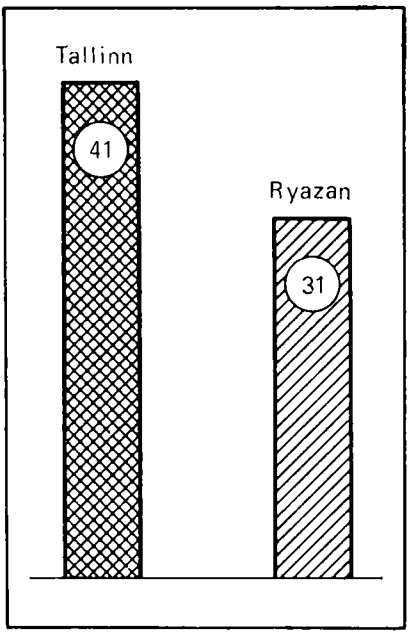

Fig. 42. Death rate from complications of atherosclerosis and hypertensive vascular disease in Tallinn and Ryazan (in per cent to the total number of autopsies)

Focal calcinosis of the aorta and coronary arteries appears in the inhabitants of Kharkov, the Baltic zone and Irkutsk in the third decade of life, and in those of Central Asia 15-20 years later. In the population of Central Asia calcinosis of the aorta and coronary arteries occurs 50-66.7 per cent less frequently than in other regions (Fig. 45). In the inhabitants of Central Asia calcinosis is much less intensive than in those of the Baltic zone and Kharkov (Fig. 46). In the women of Central Asia calcinosis of the aorta and the coronary arteries is an extremely rare occurrence, single cases of it appearing only in the fifth decade of life.

Of some interest is also the fact that atherocalcinosis occurs in the inhabitants of Irkutsk less frequently and is less severe than in those of European cities, although Irkutsk is a large industrial city.

Does it follow from the above that the geographical environment predetermines the development of atherosclerosis and that the aforementioned differences are in some measure determined by the influence of geographic conditions? Evidently, not. Considerable differences in the incidence and severity of atherosclerosis may be noted in geographically very similar areas (e.g. Tallinn and Ryazan, Ryazan and Moscow). At the same time atherosclerosis is pronounced about similarly in the inhabitants of Tallinn and Yalta.

Even within the limits of one city atherosclerosis of the coronary arteries may be unequally pronounced in representatives of diffe-

rent nationalities. Thus in Yakutsk atherosclerosis is always less strongly pronounced and is milder in the natives—Yakuts than in the non-natives, mainly Russians, living there (not less than ten years of residence in Yakutsk was taken into account). As Fig. 47 shows, coronary atherosclerosis in Yakuts at all ages both in males and females is less strongly pronounced and its development with age proceeds less intensively than in the newcomers. In most of the cases myocardial infarction also occurs less frequently in the natives (Alekseev, 1968).

Thus we now have information on the incidence of IHD in different countries, as well as within the limits of one country. Although

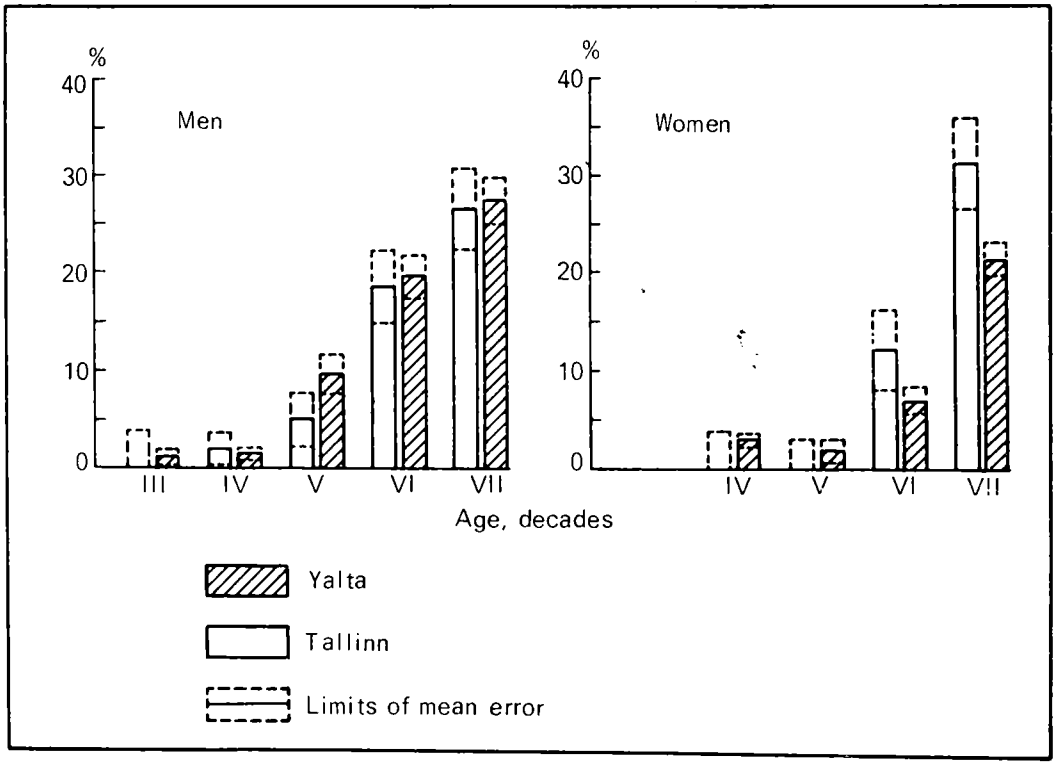

Fig. 43. Incidence of atherosclerotic stenosis of the anterior descending branch of the left coronary artery in the inhabitants of Yalta and Tallinn. Age indices in per cent to the number of investigated preparations (Lifshits)

these data are not always comparable, it may nevertheless be asserted that in some countries coronary atherosclerosis is more strongly pronounced, and the incidence of and mortality from IHD are higher than in others. Even within the limits of one country differences are observed in the anatomical manifestations of the disease, as well as in its incidence. The causes are still obscure in many respects, but it is evident that the geographic and climatic influences are overshadowed by other factors of a social and occupational character, possibly genetic ones, as well as historically formed living and

dietary conditions of the population. This question can be considerably elucidated by a study of the foregoing risk factors which we shall now deal with.

Hypercholesterolaemia

Eight years of observation in Framingham have shown that the probability of the development of myocardial infarction in men 30-59 years of age with blood serum cholesterol of 260 mg per cent and more is seven times as high as in men in whom it is not higher than

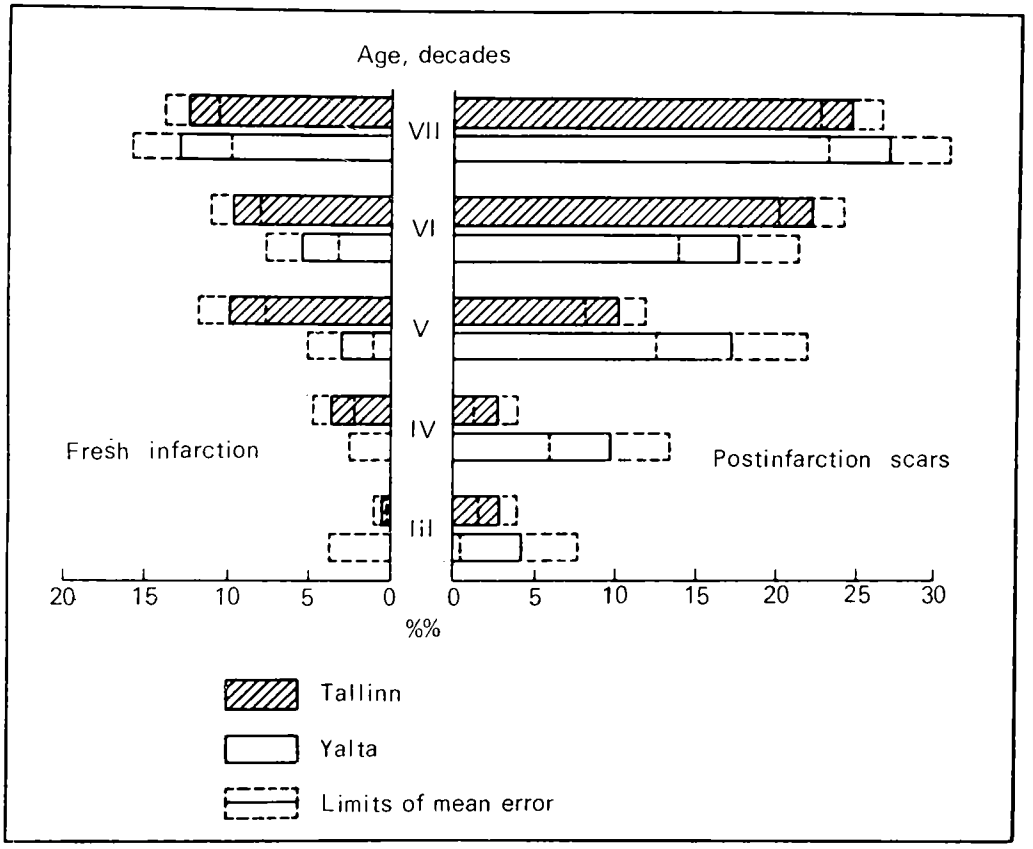

Fig. 44. Incidence of myocardial infarction in the inhabitants of Yalta and Tallinn. Age indices of men in per cent to the number of autopsies

220 mg per cent. There is no definite cholesterol limit beyond which the probability of the disease sharply increases (Kannel *et al.*, 1965). According to Westlind (1964), there is a clear correlation between the rise in the cholesterol level and the incidence of myocardial infarction. There were 4300 males at the age of 40-59 under his observation in whom there were no manifestations of IHD and diabetes was absent in the beginning of the three-year observation pe-

riod. Not one of the 270 males with 200 mg per cent of cholesterol developed myocardial infarction; of the 900 males with 250-274 mg per cent of cholesterol myocardial infarction developed in 1.4 per cent of cases; among the 800 males with 275-299 mg per cent of cholesterol new cases of myocardial infarction were recorded in 2.4 per cent; myocardial infarction developed in 3.3 per cent of the 300 males with 325-349 mg per cent of cholesterol and in 4.1 per

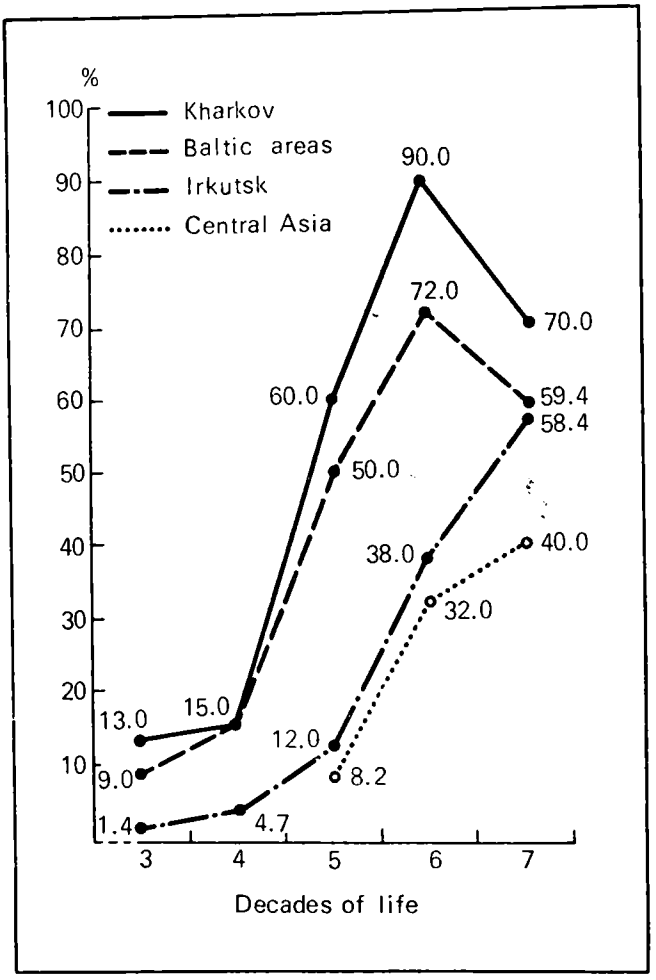

Fig. 45. Incidence of atherocalcinosis of the descending branch of the left coronary artery in males of four geographic zones of the USSR

cent of the 220 males with 350-399 mg per cent of cholesterol, i.e. the incidence of the disease regularly increased with the rise in the cholesterol content in the blood serum. A higher level of cholesterol in the blood of myocardial infarction patients was noted by Tochwicz *et al.* (1962) in Krakow. The differences were particularly striking in men at the age of 31-40 and in women at the age of 51-60. In healthy men of this age cholesterol in the blood serum amounted to 186.8 mg per cent, after an infarction (within six weeks) 226.3 mg

per cent; in healthy women its content was 211 mg per cent; and after myocardial infarction 249.9 mg per cent.

A high level of cholesterol in people who had had myocardial infarction (200 males at the age of 40-59) was also noted by Nicolaysen (1962)—an average of 300 mg per cent against 220 mg per cent in healthy people. Keys' (1963) long-term (15 years) observations on a group of business men (281 men) are very well known.

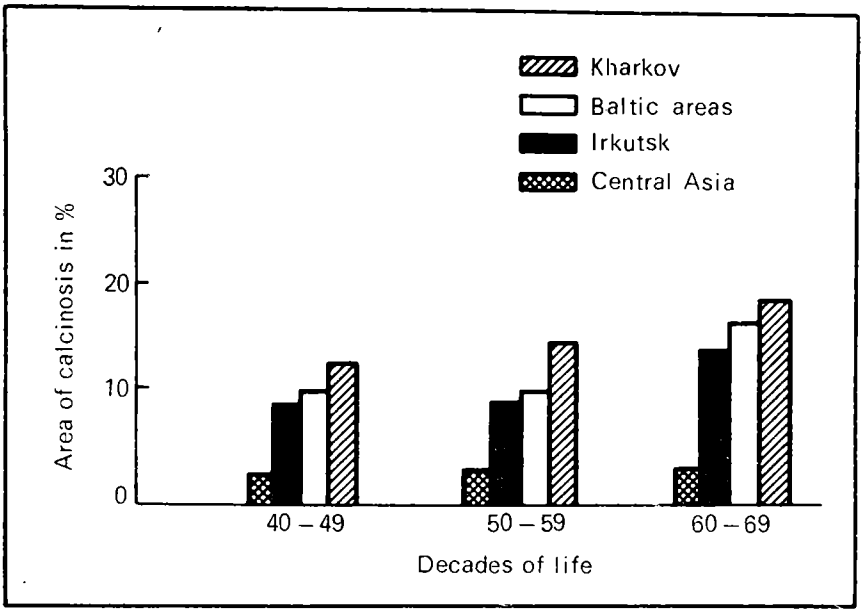

Fig. 46. Area of calcinosis of the descending branch of the left coronary artery in the inhabitants of the Baltic republics, Kharkov, Irkutsk and Central Asia

Cholesterol level in these men rose, as a rule, in the period preceding the development of myocardial infarction.

Paul *et al.* (1963) also noted a higher cholesterol level in myocardial infarction patients, the average level being 247.3 mg per cent in healthy males and 275.2 mg per cent in myocardial infarction patients. This was also confirmed by van Buchem's studies (1967) in Holland, the average cholesterol level was 237 mg per cent in healthy people and 281 mg per cent in myocardial infarction patients.

Marek *et al.* (1962) cite very interesting data. They determined cholesterol level in the blood serum of 106 people who died at the age over 20. It turned out that cholesterol in people without atherosclerosis amounted to 205 mg per cent, in those with marked atherosclerosis 240 mg per cent, and in cases of sudden death 261 mg per cent.

In examining 2659 people of both sexes in Irkutsk and Irkutsk Region Sedov (1969) found cholesterol content to be 188.9 mg per cent in practically healthy people, 222.5 mg per cent in those who suffered from coronary atherosclerosis without hypertension, and

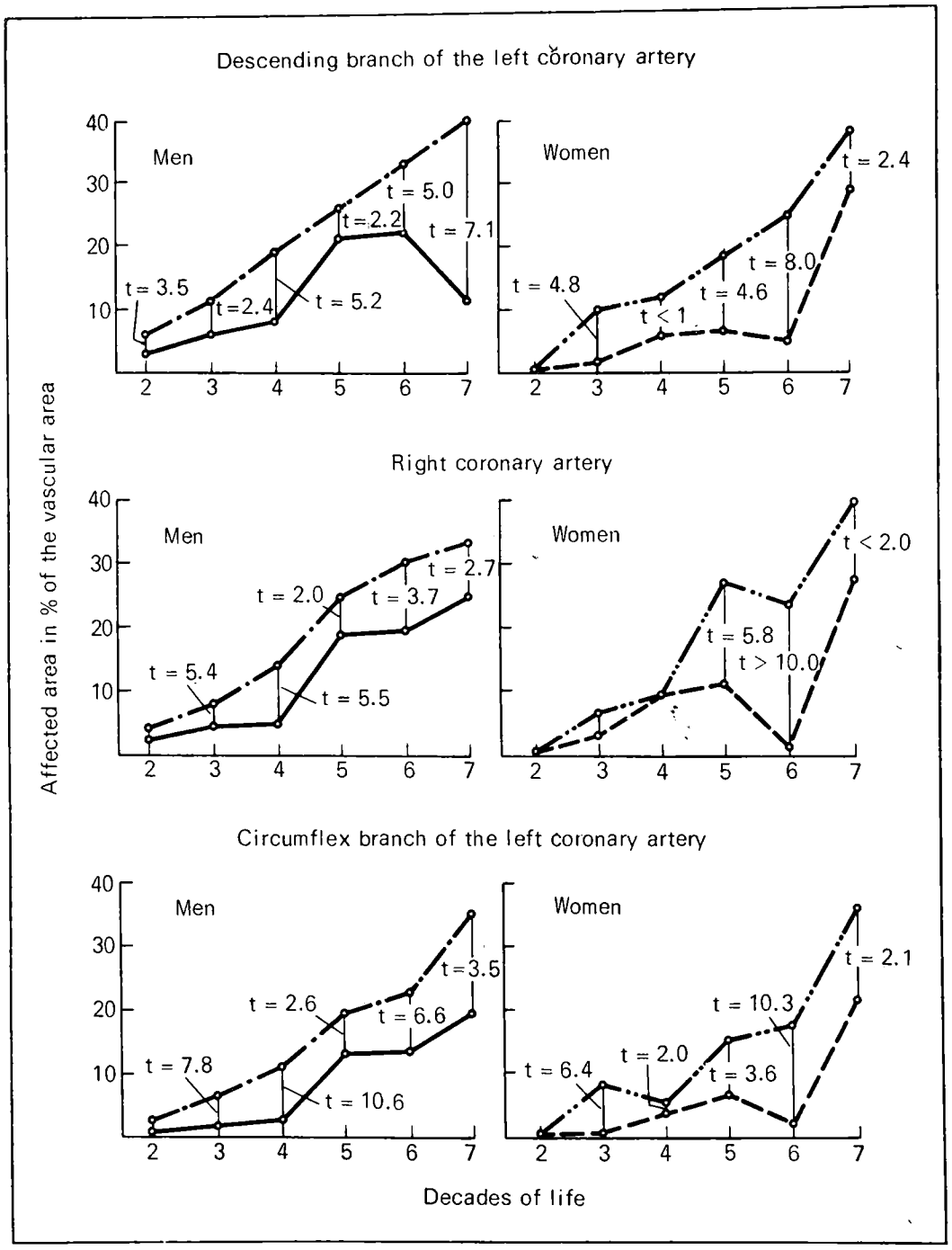

Fig. 47. Dynamics of the development of fibrous plaques in the coronary arteries of natives and non-natives (males and females) of Yakutsk

232.4 mg per cent in cases combined with arterial hypertension. Unfortunately the author did not decipher the manifestations of coronary atherosclerosis in question. In examining 650 males (natives of Andizhan) and 624 non-native males 30-59 years of age Konstantinov (1969) found coronary atherosclerosis in 3.2 per cent and

hypercholesterolaemia in 6.6 per cent of natives, and coronary atherosclerosis in 8.8 per cent and hypercholesterolaemia in 12.5 per cent of non-natives. The calorific value of the food in both groups was about the same (2774 and 2890 cal), as was also the consumption of fat (23.1 and 27.4 per cent of the daily ration), with the difference that the natives consumed only 26 per cent of animal fats and 74 per cent of cotton seed oil, whereas in the diet of the non-natives the animal fat amounted to 81 per cent.

Mingazetdinova (1969) studied three groups of males in Ufa: 1336 industrial workers, 438 engineers and technicians, and 340 scientific workers at the age of 40-59. She found a certain parallelism between the cholesterol level in the blood and IHD incidence. IHD was observed in 3.7 per cent of industrial workers, 6.9 per cent of engineers and technicians, and 9.1 per cent of scientific workers (indices standardized according to age). Cholesterol level was correspondingly the lowest in industrial workers (171.5-199 mg per cent) and the highest in scientific workers (225-232 mg per cent) (all the differences were statistically reliable). Hypercholesterolaemia over 250 mg per cent was observed only in 6.5 per cent of industrial workers and twice as often—in 13.3 per cent in scientific workers. Postinfarctional cardiosclerosis was revealed in 0.6 per cent of industrial workers and in 1.2 per cent of scientific workers. A statistically reliable rise in the cholesterol level in IHD patients, compared with healthy people, was also noted by Fodor *et al.* (1968) during examinations of males of one of the districts of Prague (247 and 240 mg per cent, respectively).

It is interesting that in cases of angina pectoris cholesterol level was always lower than in those of myocardial infarction, but higher than in healthy people. This was observed by Paul *et al.* (1963), van Buchem (1967) and earlier (1957) by Doyle *et al.* The foregoing authors and Westlind (1964) hold that hypercholesterolaemia is a prognostic sign of myocardial infarction and not of angina pectoris.

The influence of a diet with a low fat and cholesterol content and a prevalence of unsaturated fatty acids on the development of primary and recurrent myocardial infarction is noteworthy.

On the basis of several Soviet cities Glazunov (1961) showed a marked interdependence between the consumption of animal fat, the cholesterol level in the blood and the incidence of myocardial infarction. In Stalinabad, where mainly cotton seed oil is consumed, the lowest cholesterol level in the blood and the lowest incidence of myocardial infarction were observed. Ryazan held an intermediate place as regards both the cholesterol level and the incidence of myocardial infarction, whereas in Tallinn, where mainly animal fats are consumed, cholesterol level in the blood was the highest, as was also the incidence of myocardial infarction (twice as high as that among the inhabitants of Stalinabad).

Hansen *et al.* (1962) observed 133 males kept on a usual diet in a mental hospital over a period of one year and the same number

of patients of the same age who used a diet in which animal fats were fully replaced by soybean oil, while the total calories were reduced to 2000 a day. In the first group there were five myocardial infarctions and nine cases of thromboembolism of various localization, and only one attack of angina pectoris, one case of thromboembolism and not a single case of myocardial infarction in the second group. Turpeinen *et al.* (1963) and Roine (1965) cite data of their observations on patients of two mental hospitals in Finland over period of four and six years. Owing to a specially chosen diet cholesterol level was lowered in the patients of the first hospital from the average figures (250 mg per cent) at first to 220 mg per cent and then to 213 mg per cent, while the incidence of myocardial infarction amounted to 14 per 1000. In the second hospital, where the patients were on a usual diet, cholesterol level rose from 250 to 263 mg per cent and the incidence of myocardial infarction amounted to 33 per 1000. Considerable differences were also noted in the electrocardiogram. For example, in the first hospital IHD developed in 19 cases per 1000 and in the second hospital in 40 per 1000.

Ten years of observation on two groups of males of the same age yielded the following results (Chapman and Massey, 1964). In the first group (61 males), where during the first examination cholesterol level was elevated and during the subsequent examinations reduced to normal, owing to a diet, only one case of myocardial infarction was observed. In the second group (63 men) with a low initial level of cholesterol, which subsequently rose to high figures, nine new cases of myocardial infarction were observed in the course of the same ten years.

Walker and Gregoratos (1967) observed 2450 whites at the age over 20 who were sentenced to long prison terms in the South African Republic and kept for five years on a 'Bantu diet' with a low animal fat content. There were only three cases of myocardial infarction with but one fatal outcome among them. Among the white population of Johannesburg of the same age these figures are about eight times as high.

In his last study Keys (1963) cites the results of five years of observation on 1347 Greeks and Yugoslavs at the age of 40-59 who used mainly olive oil in their food. The average cholesterol level in them did not exceed 200 mg per cent. Only five fatal outcomes of myocardial infarction were observed. At the same time, according to statistics, there would have been about 30 deaths from myocardial infarction among men of the same age living on the usual 'American diet' in the USA.

Of considerable interest is the experiment of the so-called New York Anticoronary Club which began to function in 1957. The experiment is based on a diet which leads to a lowered cholesterol level of the blood. Two types of diet were elaborated, namely, a 'prudent' diet (2000-2700 cal) for persons with a normal body weight, and a 'reducing' diet (1600 cal) for overweight persons to keep to

temporarily. In the first diet 23-26 per cent of the calories were furnished by proteins, 42-45 per cent by carbohydrates, and 30-38 per cent by fats (7-8 per cent by saturated fatty acids); in the second diet 35 per cent of the calories were furnished by proteins, 45 per cent by carbohydrates, and 19 per cent by fats (7.8 per cent by saturated fatty acids). The diet of the second type ensured a daily deficit of about 1000 calories and a weekly weight reduction of up to 2.5 kg. In seven years the average cholesterol level in the group of people kept on a diet was reduced from 260 to 225 mg per cent and the incidence of new myocardial infarctions amounted to 1.96 per 1000 in the age group of 40-49 and 3.79 per 1000 in the age group of 50-59, whereas in the control group, where cholesterol level remained practically unchanged (250 and 252 mg per cent) these figures were 6.47 per 1000 for the 40-49 age group and 13.31 per 1000 for 50-59 age group. In Framingham the figures were close to the latter (6.47 and 18.55, respectively) as also in Albany (6.94 and 18.7) (Rinzler *et al.*, 1956, and Chrisakis *et al.*, 1965). In summing up these observations Rinzler points out that among people kept on a diet there were 430 new cases of myocardial infarction per 100 000 population as against the 1025 cases in the control group.

The results obtained by the Anticoronary Club were confirmed by the study of Dayton *et al.* (1969) whose findings were published. The authors observed for eight years two groups of volunteers—middle-aged and elderly males. The control group numbered 422 and the experimental group—424 males 50-89 years of age (about half their number were under the age of 64). The groups were chosen very carefully with regard to nationality, height and body weight, mean systolic and diastolic pressure (in the control group the mean systolic pressure was 136 mm Hg and the diastolic pressure 77.1 mm Hg; in the experimental group it was 136.5 and 78.2 mm Hg), the initial cholesterol level in the blood serum (234.3 and 232.7 mg per cent) and total lipids in the blood (864.5 and 852.5 mg per cent). The control group was kept on a diet in which 40 per cent of the calories were furnished by fat, mainly animal. In the experimental group 40 per cent of the calories were also furnished by fats, but two-thirds of them were vegetable oils. In the diet of the control group linoleic acid correspondingly amounted to 10 per cent and to 38 per cent in the experimental group. The cholesterol content in the experimental group was 38 per cent. The cholesterol content in the diet of the experimental group was reduced to 365 mg per day as against the 653 mg in that of the control group. Among the people who died 80 per cent were subject to autopsy. An average of 12.7 per cent decrease in cholesterol compared with its initial content was observed in the experimental group already in four months. The content of linoleic acid in the subcutaneous adipose tissue of the experimental group subsequently increased from 10.9 to 33.7 per cent. Over a period of eight years the following was observed in the control and experimental groups: latent myocardial infarctions

(four and nine cases), myocardial infarctions with a manifest clinical picture (40 and 27), sudden coronary death (27 and 18), cerebral infarction (22 and 13). The summary difference between the groups is statistically reliable ($p<0.01$) as are also the differences in the fatal outcomes underlied by atherosclerosis (70 and 48, respectively; $p<0.05$). The highest prophylactic effect was noted in the younger age groups (under the age of 65). At the same time there were no considerable anatomical differences or differences in the markedness of atherosclerosis in the coronary or other vessels.

Studies have also been conducted tracing the influence of the decreased cholesterol in the blood on the development of recurrent myocardial infarction. Nelson (1956) was the first who showed the favourable influence of its decrease. He found that of the patients, who survived myocardial infarction and in whom blood cholesterol decreased an average of 10 per cent under the influence of a diet with a low content of fat and cholesterol, mortality from a recurrent infarction in the course of five years was 9.1 per cent, whereas among the patients unamenable to the influence of a diet it amounted to 32 per cent.

Morrison (1960) cites still more convincing data. Of 100 myocardial infarction patients who were kept on a diet containing 15 per cent fat and 50-70 mg of cholesterol 38 lived for another 12 years, whereas 100 other patients who were on a usual American diet died much sooner. In the former a decrease in the mean cholesterol figures from 312 to 220 mg per cent and a mean decrease of 8-10 kg in weight were observed.

Bierenbaum *et al.* (1965) obtained analogous data during five years of observations on persons who had survived myocardial infarction: recurrent infarctions and fatal outcomes were encountered 37.5 and 60 per cent less frequently among persons who kept to a diet with a low fat content which caused the initial cholesterol level to lower about 10 per cent.

Leren (1966, 1967) from Oslo reported his observations over a period of five years on two groups of males (206 each) who had survived myocardial infarction. The groups were chosen at random. One of them was on a diet with a low content of animal and vegetable fat, the other group was on a usual diet. A rapid decrease in the cholesterol content, averaging 17.6 per cent of the initial 296 mg per cent was observed in the first group (only 3.7 per cent also of the initial 296 mg per cent in the control). In the first group 34 patients had 43 new infarctions (ten ending fatally); in the control group 54 patients had 64 new infarctions (23 with fatal results). The author finds that a diet produces the most favourable effect at the age of 60.

Thus the favourable influence of a lowered cholesterol level in the blood through a diet in preventing myocardial infarction is no longer doubted today. We adhere to this point of view, although there are some studies whose authors did not observe such an effect.

They also did not note an unfavourable effect of a diet that ensures a lowered cholesterol level in the blood (Watson, 1963; Rose *et al.*, 1965; report of the Research Committee).

The role played by blood triglycerides in the development of atherosclerosis, including IHD, is being widely discussed of late. Some researchers hold that the content of triglycerides plays an even more important diagnostic and prognostic role than that of cholesterol. Berkowitz (1963), for one, found hypertriglyceridaemia in 72 per cent and hypercholesterolaemia in only 41 per cent of 100 IHD patients. Schrade *et al.* (1960) also found hyperglyceridaemia in 71 per cent of IHD patients. Albrink (1962) points out that 50 per cent of IHD patients have no hypercholesterolaemia, while 82 per cent of the patients observed by him exhibited increased content of triglycerides. Without going into details we only point out that a single prospective epidemiological study failed to elucidate this question. In Albany Brown *et al.* (1957) observed 1851 males over a period of four years and managed to compare the prognostic significance of the increase in the content of cholesterol and triglycerides; 70 (4 per cent) of males 50-65 years of age had nearly three times the normal content of triglycerides (14.1 mEq/l), five developed IHD. Hypercholesterolaemia was also observed in 4 per cent, and only 13 developed IHD. Furthermore, of the 939 persons with 5.2 mEq/l of triglycerides 27 developed infarction (i.e. 29 per 1000 over period of four years), while of the 772 persons with more than 5.2 mEq/l of triglycerides 29 persons developed infarction, i.e. 38 per 1000. However, the former had an average of 216 mg per cent of cholesterol in the blood and the latter 236 mg per cent. Long-term observations are required to make sure which of these factors is of greater prognostic importance.

We cannot help mentioning the study of Rosenman *et al.* (1966) who hold that there is a possibility of predicting the relative or absolute immunity to IHD. During the four years of observation not a single man with a cholesterol content below 225 mg per cent, triglycerides less than 126 mg per cent and a β-α-lipoprotein ratio below 2 developed myocardial infarction.

Arterial Hypertension

The influence of elevated arterial pressure on the development of IHD was clearly revealed in Framingham by Dawber *et al.* (1959). They write that for both men and women a rise in arterial pressure from the minimum systolic pressure of 120 mm Hg to 180 mm Hg increases the IHD risk about seven-fold. In persons with the blood pressure below 120 mm Hg on first examination the incidence of IHD is but one-fourth of that assumed for the given age and sex.

Extremely convincing in this respect are the observations of Spain *et al.* (1963). They studied the IHD incidence among 6000 men who were nearly of the same ethnical, cultural, and economical level

and had more or less similar diet. It turned out that among the 4937 males with normal blood pressure (normotensives) the IHD incidence was only 7.4 per cent as against the 15 per cent among the 838 persons with elevated blood pressure (hypertensives): moreover, this difference was the most strongly pronounced under the age of 50—12.3 per cent against 4.4 per cent among normotensives, i.e. nearly three times as high. At 50-65 years of age these figures were 17.4 and 9.9 per cent, respectively.

Analogous data on the role of elevated blood pressure in the development of IHD were also obtained in a prospective epidemiological study in Albany (Doyle *et al.*, 1964). They show that in cases of a combined increase in weight (40 per cent and more above the average), 275 mg per cent and higher of cholesterol and a diastolic pressure of 110 mm Hg and higher the probability of the IHD development increases. Morris and Crawford (1958) also found that elevated blood pressure and increased cholesterol influence the development of IHD; of 147 men with a mean systolic pressure of 176 mm Hg a mean cholesterol content of 272 mg per cent IHD developed in 25 in the course of five years, whereas of the 150 men with normal mean indices (131 mm Hg blood pressure and 205 mg per cent of cholesterol) it developed only in one.

According to Deming (1968), if the systolic pressure rises to 158-167 mm Hg and the diastolic to 98-102 mm Hg, mortality increases three-fold. In persons with a systolic pressure of 160-179 mm Hg the risk of IHD development increases 50 per cent and with a pressure above 180 mm Hg nearly 150 per cent.

At the same time Chapman and Massey (1964) hold that hypercholesterolaemia has a direct bearing on the development of myocardial infarction, and hypertension on that of angina pectoris.

It is, of course, possible that the character of hypertension, its constancy to be exact, is also of some significance. Berkson and Stamler (1965) cite the results of their long-term observation on 290 patients under the age of 46 with an arterial pressure of 160/95 mm Hg and higher. The patients were divided into two groups; in the first group the arterial pressure was permanently high, in the second the diastolic pressure was below 95 mm Hg during rest and sedative therapy. In the first group mortality was 54 per cent among women and 75 per cent among men; in the second group it was 13 per cent and 28 per cent, respectively.

From the pathological point of view there is every reason to believe that hypertension negatively affects the course of atherosclerosis and, consequently, of IHD, since in experiment it accelerates the atherosclerotic process. In experiment this was shown by Wilens (1951); Wissler *et al.* (1954); Volkov (1956); Adel *et al.* (1962); Heptinstall *et al.* (1962); Stephenson *et al.* (1962); Smolensky (1964), and Kasatkina (1969).

The studies in epidemiology of atherosclerosis conducted in the Soviet Union on the basis of pathological data have clearly revealed

an accelerating influence of hypertension on the development of coronary atherosclerosis and its severity (Vikhert and Matova, 1967). The right coronary artery and the anterior descending and circumflex branches of the left coronary artery of 887 people died at the age of 30-69 (568 men and 319 women) were studied. Of these people 486 suffered from hypertensive vascular disease (the first group) and 401 died of various complications of atherosclerosis without hypertension (the second group). Controls of 1983 cases (the third group) were the vessels of so-called practically healthy people; they died of accidental causes, had no scars in the myocardium, and no cysts in the brain, their hearts weighed not more than 400 g in men and 350 g in women; they were not affected by any chronic diseases.

Atherosclerotic changes in the aorta were found in 56 per cent of healthy males in the fourth decade of life. In the group of people who died of complications of atherosclerosis, but not suffered from hypertension, changes in the aorta were found in 70 per cent of autopsies, while in cases with both hypertensive disease and atherosclerosis in 82 per cent of autopsies. The frequency of discovery of atherosclerosis progressed with age. At the age of 60-69 practically 100 per cent of people (both healthy and ill) have atherosclerosis of the aorta. The number of severe forms of the affection also increases with age, most commonly in patients with both atherosclerosis and hypertension.

Atherosclerotic changes in the coronary vessels, in particular the anterior descending branch of the left coronary artery, are found more often than in the aorta even in practically healthy people. At the age of 30-39 71 per cent of healthy people have atherosclerosis of the coronary arteries; at the age of 70-80 the incidence of coronary sclerosis rises to 97 per cent. In the first two groups coronary sclerosis was found in 100 per cent. The incidence of complicated changes and calcinosis increases with age.

The intensity of atherosclerosis increases simultaneously with its incidence. These two processes run parallel to each other, the area of atherosclerotic changes in the coronary arteries increasing with age (Figs. 48 and 49). In cases of hypertensive disease coronary sclerosis manifests itself more intensively than in practically healthy people at all age periods and in all the coronary arteries studied. But whereas these differences between hypertensives and practically healthy people are statistically reliable, between hypertensives and normotensives they are reliable only for the right coronary artery (Fig. 49) and the circumflex branch of the left. As regards the anterior descending branch, it may be a question only of a tendency toward an increase in the area of affection (Fig. 48). A marked involvement in the process not even of all the coronary arteries is also undoubtedly very important since it reduces the accommodation potentialities of the coronary blood flow. At the age of 50-59 a mild affection of the descending branch of the left coronary artery (in-

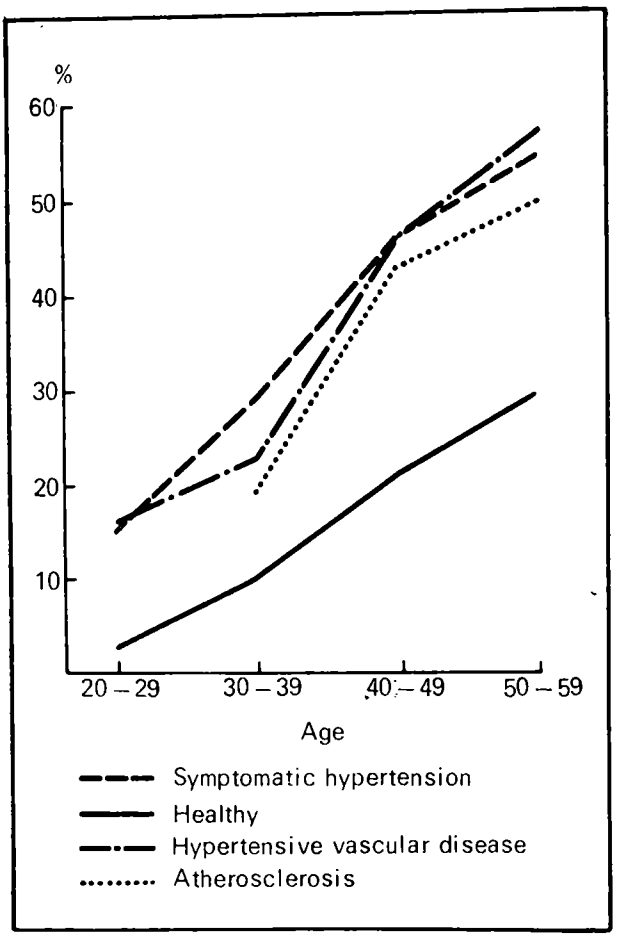

Fig. 48. Area of atherosclerotic changes in the descending branch of the left coronary artery in various forms of hypertension, atherosclerosis and in practically healthy people

volving in the process up to 33 per cent of the vessel's area) was observed in 35 per cent of practically healthy males, a moderate affection (involving 33-50 per cent of the area) in 50 per cent, and a severe affection (more than 50 per cent of the area) in 15 per cent. Those who died of complications of atherosclerosis with normal blood pressure had a mild affection in 13 per cent of cases, a moderate affection in 35 per cent and a severe affection in 52 per cent. In patients with hypertensive vascular disease and atherosclerosis mild affection of the coronary arteries was found in 3 per cent only, a moderate affection in 28 per cent and a severe affection in 69 per cent of cases (Fig. 50).

The greater severity of atherosclerosis of the coronary arteries in cases of hypertensive vascular disease is also evidenced by a considerable incidence of stenoses of one or more branches. During the fifth decade of life stenoses of the coronary vessels in males with hypertension occur twice as often as in males with normal blood pressure (35 per cent and 18 per cent) (Table 6). In elderly men the differences are not so great, while in women they are not statistically reliable.

Some authors hold that atherosclerosis is intensified only in cases of essential hypertension, while symptomatic hypertension in man has an opposite, inhibitory influence on the atherosclerotic process since such complications as angina pectoris and myocardial infarction are rare among patients with symptomatic hypertension (Ratner and Spivak, 1960).

As a matter of fact, patients with nephrogenic hypertension, mainly with nephritis, seldom die of acute coronary failure, myocardial infarction and cerebral haemorrhage. Among 160 our patients

who suffered from both nephritis and arterial hypertension and died at the age under 60 myocardial infarction was the cause of death only in two cases (1.2 per cent). Postinfarctional scars were found in five persons (3 per cent) and cerebral haemorrhage in 13 (8 per cent). In the rest of the cases the cause of death was uraemia. However, the results of biometric evaluation of the vessels of patients who died of nephrogenic hypertension at the age of 30-39 showed that atherosclerosis of the aorta and coronary arteries in them was more strongly pronounced than in cases of essential hypertension and greatly exceeded the atherosclerotic changes in those who died of atherosclerosis with normal blood pressure and in practically healthy people. After the age of 40 the differences in intensity of atherosclerotic changes in the coronary arteries in hypertensive vascular disease and symptomatic hypertension disappear.

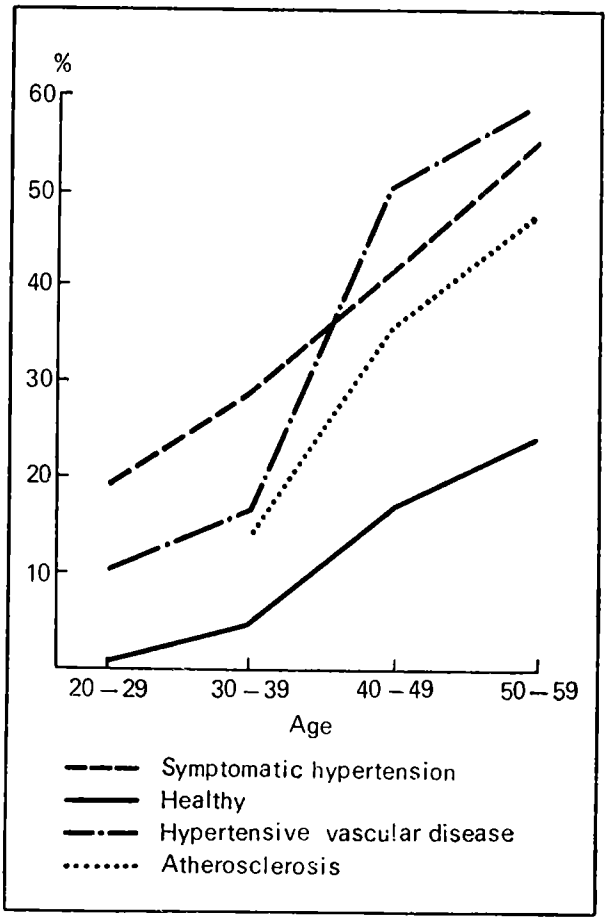

Fig. 49. The same in regard to the right coronary artery

It is extremely interesting that in all age groups of persons with symptomatic hypertension coronary stenosis occurs less frequently than in persons who died of atherosclerosis with or without hypertensive disease (see Table 6). The differences between the first two groups and the third group are statistically reliable.

It is possible that precisely the rareness of stenosing atherosclerosis accounts for the almost total absence of fatal myocardial infarction cases of patients with symptomatic hypertension and the infrequent discoveries in them of postinfarctional cardiosclerosis.

Analogous results were obtained by Sternby (1968). The author arrives at the following conclusion: coronary atherosclerosis in all age groups of both men and women is more strongly pronounced in persons with hypertensive vascular disease. It is particularly strongly pronounced at the age under 70.

Thus the foregoing data undoubtedly indicate an intensifying

influence of hypertensive vascular disease on the course of atherosclerosis and, especially, on the development of its exacerbated and severe forms. This apparently plays an important role in the development of clinical manifestations of IHD.

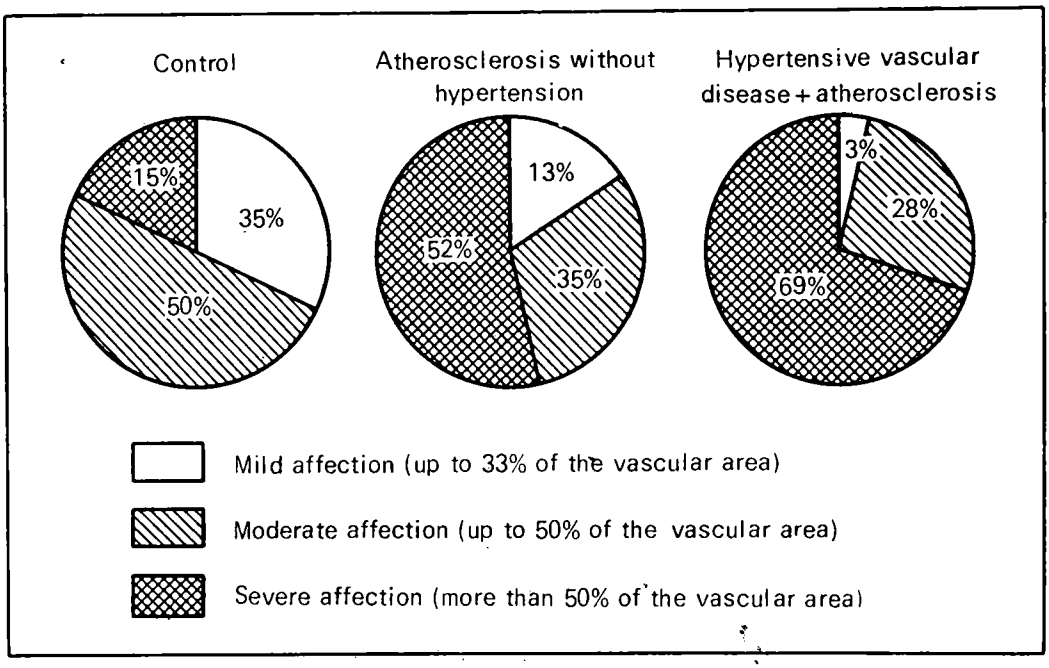

Fig. 50. Incidence of various degree of affection of the descending branch of the left coronary artery in 50-59-year-old males

Table 6. The Incidence of Stenoses of Coronary Arteries (in Per Cent to the Number of Cases of the Given Age Group)

Disease	40-49 years		50-59 years		60-69 years	
	M	F	M	F	M	F
Hypertensive vascular disease	35	Single autopsy cases	55	40	58	55
Atherosclerosis (without hypertension)	18	Same	45	37	49	48
Symptomatic hypertension	4	Same	17	13	37	23

Smoking

To understand correctly the role of smoking in IHD the following factors must be taken into account:

1. Nicotine causes a certain rise in blood pressure, tachycardia, an increase in the stroke volume and, especially, in cardiac output (up to 200 per cent of the initial level).

Usually IHD develops in persons with far advanced atherosclerosis in the presence of rigid and stenosed coronary arteries, for which reason any increase in the oxygen requirement of the myocardium may lead to the development of a relative coronary failure. Rinzler *et al.* (1956) showed that in people with coronary atherosclerosis inhalation of a cigarette smoke increases the work of the left ventricle by 30 per cent without a corresponding increase in the coronary blood flow. Moreover, after administering nicotine to rabbits with experimental coronary atherosclerosis these authors observed even a decrease in the coronary blood flow.

2. Bellet *et al.* (1960) produced stenosis of the coronary arteries in dogs by applying a casein ring on them. In normal dogs nicotine caused an increase in the coronary blood flow by 125 per cent and in experimental dogs only by 83 per cent. On this basis the authors conclude that in cases of stenosis of the coronary arteries the latter cannot provide for the increased oxygen requirement of the myocardium, and nicotine only aggravates this insufficiency.

Kaverina (1958) holds that in healthy people the narrowing of the coronary arteries under the influence of nicotine is compensated by a rise in blood pressure owing to which the volume of the inflowing blood even increases. In atherosclerotic affection of the vessels the narrowing caused by nicotine is no longer compensated, and the blood supply to the myocardium deteriorates.

3. Smoking as such fosters the development of coronary atherosclerosis. Studies dealing with this question are few, but fairly convincing. Avtandilov *et al.* (1965), employing the planimetric method, studied the coronary vessels of 180 smokers and 220 non-smokers and found that the area of the intima affected by atherosclerosis in smokers is two or three times as large as in non-smokers. Moreover, in smokers severe stenosing forms are found about twice as often (36.1 per cent in smokers and 19.1 per cent in non-smokers).

Sedov (1966) studied the coronary arteries by the method suggested by the WHO in 1026 smokers and 290 non-smokers (males). Atherosclerosis was found more frequently in smokers in all the three branches (the anterior descending branch 96.8 and 92 per cent, the circumflex branch 88.1 and 80 per cent, the right coronary artery 89.5 and 82.8 per cent, respectively). The area covered by fibrous plaques in most of the age groups was also larger in smokers, this difference being statistically reliable in most cases of the middle and older age groups, as can be seen from the example of the anterior descending branch of the left coronary artery (Fig. 51).

In young people, apparently in connection with a short smoking record, the difference is slight, as it is also in the eighth and ninth decades of life. In old people this is possibly associated with a small number of observations or with a certain resistance to the action of nicotine in some people, the sensitive ones having died of IHD earlier. The atherosclerotic process in smokers was not only of a greater extent, but also more severe, stenosis of the coronary arte-

ries with more than 50 per cent narrowing of the lumen having been found in 10.1 per cent of smokers and 6.2 per cent of non-smokers.

Indications of a higher incidence and greater severity of atherosclerosis in smokers can also be found in the study of Auerbach *et al.* (1965). They studied the coronary arteries of 126 men who never smoked and 893 cigarette smokers. According to their findings, the severity of coronary atherosclerosis depends not only on smoking, but also on how many cigarettes a day are smoked. For example, at the age 45-59 the incidence of severe coronary atherosclerosis in non-smokers was 7.1 per cent, in those who smoked up to 20 ci-

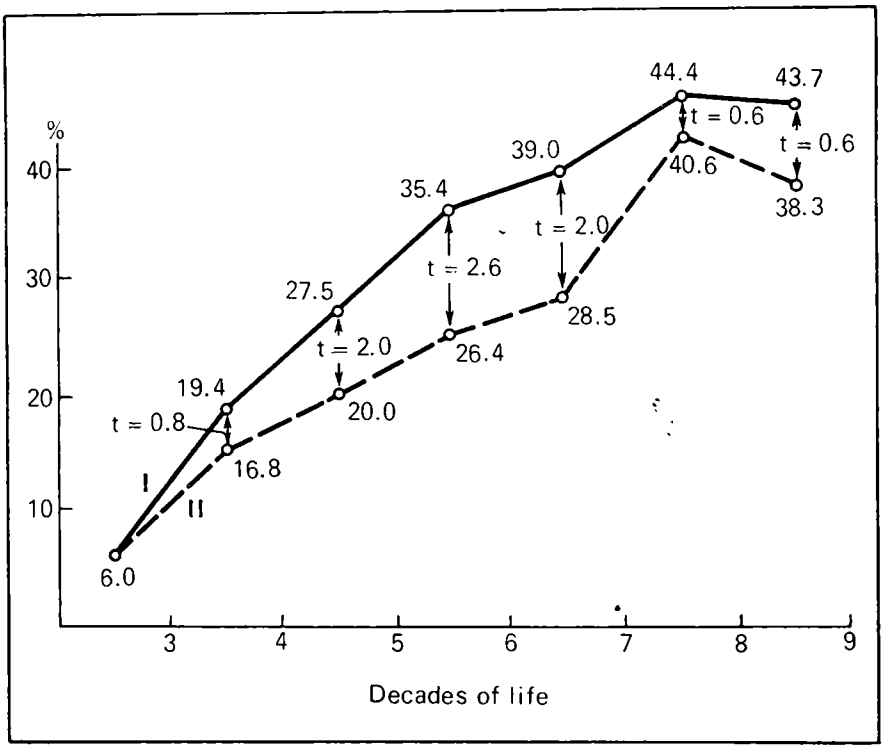

Fig. 51. Area of the intima in the descending branch of the left coronary artery covered by fibrous plaques in male smokers (I) and non-smokers (II)

garettes a day 19.6 per cent, from 20 to 30 cigarettes 24.6 per cent and more than 40 cigarettes 28.6 per cent. These correlations persisted at all age periods, and the indices standardized according to age were 15; 29.2; 37.4 and 45.9, respectively. In smokers severe coronary atherosclerosis developed 10-15 years earlier than in non-smokers.

The negative influence of smoking on blood supply to the myocardium was extensively confirmed by a number of epidemiological studies which recognized smoking as one of the leading risk factors in IHD. We have already mentioned Sedov's study above. In mass examination of the population of Irkutsk he found that in smokers the level of cholesterol was 197.5 mg per cent, of β-lipoproteins

62.9 per cent and 199.5 mg per cent of phospholipids, whereas in non-smokers the indices were 179.2 mg per cent, 58.3 per cent and 203.6 mg per cent, respectively (the differences in the cholesterol and β-lipoprotein content are statistically reliable). The syndrome of angina pectoris of effort was found in 26.8 and atherosclerotic heart disease in 127.1 of smokers, and only in 16.3 and 90.2, respectively, of non-smokers per 1000 population.

Long-term observations in Framingham (and also in Albany) showed that the incidence of myocardial infarction among smokers of 20 and more cigarettes a day is three times as high as among non-smokers. According to Stamler (1963), this correlation varies between 2.3 and 5.4 at different age periods. Shapiro *et al.* (1965) point out that men smoking two and more packs of cigarettes a day run six times as great a risk of developing myocardial infarction as do non-smokers. Of the 133 coronary thrombosis patients at the age under 50 only 22 did not smoke at all or smoked a pipe or cigars; the other 111 patients smoked cigarettes.

Oram *et al.* (1963) mentioned the influence of smoking not only on the incidence of IHD, but also on its course; mortality from myocardial infarction among men at the age of 45-54 smoking ten cigarettes a day was 2.4 times as high as among non-smokers, among those smoking 10-39 cigarettes a day it was 3.1 times as high, and among smokers of 40 and more cigarettes a day 3.4 times as high. Similar regularity was also observed in women; mortality from IHD among those smoking 20-39 cigarettes a day was 2.7 times as high as among non-smokers. Among older people these differences were not so strongly pronounced. Smaller differences among older smokers and non-smokers are also mentioned by Borhani *et al.* (1963) who associate this with addition of other risk factors in elderly people.

It is noteworthy that epidemiological studies have not revealed any correlation between smoking and the incidence of angina pectoris. In Framingham there was no correlation, while in Albany even a negative (but statistically unreliable) connection was observed. Von Ahn (1960) pointed out that even continuous smoking of one cigarette after another seldom led to angina pectoris. Oram and Sowton (1963) found its direct connection with smoking a cigarette only in 1 per cent of angina pectoris patients.

Of still greater interest are the findings of epidemiological studies on how the giving up of smoking affects the development of IHD. The incidence of IHD and fatal outcomes among people who have given up smoking does not differ from that among people who did not smoke before. Doyle *et al.* (1964) (Framingham and Albany) and Epstein (1967) (Tecum-seh) arrived at the same conclusion on the basis of long-term epidemiological studies. Shapiro *et al.* (1967) also point out that men who have given up smoking run about the same risk of developing myocardial infarction in the next five years as those who never smoked.

The reason for this is not clear since coronary atherosclerosis, as we have already mentioned, is much more strongly pronounced in smokers. The decrease in the risk as regards myocardial infarction in those who have given up smoking is connected apparently with elimination of the functional factors in the disturbance of coronary circulation and once more evidences that the latter play an important role in the development of IHD.

The adverse influence of smoking is also connected apparently with a rapid liberation of catecholamines by the adrenals and sympathetic ganglia, including the cardiac ganglia, upon intake of nicotine (Watts, 1960; and Kershbaum *et al.*, 1962).

With liberation of catecholamines is connected another effect of smoking, namely, the mobilization from the fat depots of free fatty acids and the increase in their concentration in the blood serum. This effect of nicotine can be excluded by blocking the sympathetic ganglia (Kershbaum *et al.*, 1962).

Moreover, the same authors, and also Bellet *et al.* (1962), note that the influence of nicotine on the level of free fatty acids is stronger and the effect lasts longer in people who had myocardial infarction than in healthy people.

At the same time most authors now deny any connection between smoking and the level of other blood lipids, especially cholesterol (Doyle *et al.*, 1959; Bellet *et al.*, 1962; Kershbaum *et al.*, 1962; Konttinen, 1962; Mustard and Murphy, 1963, and Heyden, 1966).

It is also necessary to mention the point of view of Harkavy and Perlman (1960) who explain the connection between smoking and IHD by an allergy the smokers have for different components of tobacco. Affection of the coronary arteries and the myocardium was observed in experiment in rabbits sensitized by tobacco from which the nicotine had been extracted, while perfusion with a solution of tobacco extract containing no nicotine resulted in constriction of the coronary arteries. Moreover, in persons with a positive allergic skin reaction to tobacco disorders of coronary circulation were observed ten years earlier than in those with a negative skin reaction (56 and 65 years of age, respectively). This problem, however, requires further study.

At the same time it is perfectly clear that cigarette smoking is one of the most important risk factors in IHD. The causes of this phenomenon are in many respects still obscure; in particular, it is absolutely incomprehensible why smoking of cigarettes is more harmful than that of Russian papirosy, cigars, etc.

Physical Acitivity

The role of this factor in the development of IHD is giving rise to many contradictory opinions. The epidemiological findings are also contradictory and heterogeneous.

The data obtained in Framingham are in favour of physical acti-

vity as a factor that prevents the development of IHD, the risk of dying of various manifestations of coronary insufficiency being three times as high in physically less active men. Well-known are also Morris' (1960) comparative data on the incidence of myocardial infarction in bus conductors whose work is more active as compared to that of bus drivers whose work is less active, this incidence being twice as high in the latter. He found similar correlations in his study of the IHD incidence among clerks and letter-carriers. Myocardial infarction with fatal outcome was observed twice as often in the former as in the latter[1]).

Studies of postal workers engaged in sorting letters (sedentary, inactive work) and letter-carriers (Kahn, 1963) yielded analogous results; mortality was 40-90 per cent higher in the former than in the latter. Similar data are cited by Shapiro *et al.* (1965). The risk of developing myocardial infarction was 61 per cent higher in the less active than in the more active. Lukel *et al.* (1959) note that IHD is encountered 50 per cent less frequently in physically hard working farmers than in people of sedentary occupations.

Brunner *et al.* (1962) also mention a lower IHD incidence among manual workers. There were 8500 members of an agricultural cooperative in Israel at the age of 40-65 under observation for ten years. The ratio of IHD incidence and mortality from this disease among the manual and sedentary workers was 3 : 1.

McDonough *et al.* (1965) mention greater differences in IHD incidence among small tenant farmers (physically more active) and farm-owners, as well as between small and large farm-owners (the ratio was about 1 : 3 in both cases).

The results of four years' observations on 110 000 men and women at the age of 25-64 are cited by Franc (1968) (the so-called Health Insurance Plan). All these people were examined repeatedly. During the observation period 881 males died of primary myocardial infarction. The incidence of primary infarction was much higher among the physically inactive people. The mortality among them was also twice as high as among the physically active people (44 and 21 per cent, respectively); it follows that the chances of a fatal infarction were four times as high in the physically inactive as in the active people.

Smoking considerably increases the risk of developing myocardial infarction irrespective of physical activity. This applies only to

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1) These studies have met with a number of objections. First of all it was shown (Oliver, 1967) that bus-driver apprentices at the age of 21-25 differ in their physical make-up from the conductor apprentices, they are taller, have larger chests, a thicker subcutaneous adipose layer, a higher level of cholesterol in the blood and weigh more (all these differences are statistically reliable). It is possible that in virtue of their constitutional features alone the drivers are more susceptible to IHD than are conductors. Moreover, it is possible that finding their work too hard the conductors quit their jobs, i.e. disappear from the researchers' field of vision.

the incidence of the disease and not to mortality from it; infarction occurred more frequently in smokers, but during the first month mortality from it was higher among physically inactive people. Smoking combined with physical inactivity increases the risk of fatal infarction in these people five-fold compared with physically active people who do not smoke.

A large number of studies aimed at elucidating the role of occupational factors in the development of coronary atherosclerosis has of late been conducted in the Soviet Union. In Novokuznetsk Goldberg (1964) studied the incidence of coronary atherosclerosis among 7341 men 30-59 years of age. It turned out that among those whose work was connected with considerable nervous strain and little physical activity the incidence of coronary atherosclerosis was more than 50 per cent higher (22.4 against 9.9 per 1000) than in the examined people who worked physically (the data have been standardized according to age) and the incidence of myocardial infarction was three times as high (9.1 and 2.9 per 1000, respectively). Similar data are cited by Barats (1964): the incidence of coronary atherosclerosis among male mental workers at one of the Sverdlovsk enterprises was 3.41 per cent as against 1.23 per cent among manual workers. Among the latter hypertensive vascular disease occurred 33 per cent less frequently and hypercholesterolaemia 50-60 per cent less frequently than among the former.

On the basis of examining the male population of the Bauman District of Moscow Kalinina and Bogoslovsky (1964) have also arrived at the conclusion that among office workers (i.e. physically inactive people) the incidence of myocardial infarction is twice as high as it is among industrial workers.

On analysing the incidence of myocardial infarction in various districts of Kiev Krister *et al.* (1964) concluded that it is highest (50-100 per cent higher than average) in the districts where office workers constitute the bulk of the population. Baubine (1964) also pointed out a higher incidence of myocardial infarction among mental workers of Kaunas, both men and women. Mingazetdinova (1969) examined three groups of men 40-59 years of age. The first group embraced 1136 industrial workers who did manual work during the working day; the second group included 438 engineers, technicians and administrative workers, and the third group 340 scientific workers whose professional endeavours involved continuous neuropsychic strain and no physical efforts. Ischaemic heart disease was found in 3.9 per cent of people of the first group, 6.5 per cent of the second group, and 8.6 per cent of the third, i.e. the ratio of the first and third groups was 1 : 2. At the same time the mean level of serum cholesterol was the highest among the scientific workers (at the age of 50-59 230.2 mg per cent as compared with 214.9 mg per cent in the second group and 184.1 mg per cent in the first). Hypercholesterolaemia above 250 mg per cent was observed in 13.3 per cent of scientific workers and only in 6.5 per cent of industrial

workers. The same thing applied to hypertension; 160/95 mm Hg and higher in 14.5 and 8 per cent, respectively.

There are pathoanatomical data that seem to indicate a favourable role of manual work in preventing coronary atherosclerosis. In studying at the autopsy the vessels of 650 men as far back as 1935 Rapoport discovered considerable differences in the extent of coronary atherosclerosis depending on the occupational factor. Severe forms were observed most frequently in mental workers (29.4 per cent), rarer in people whose occupations involved light or hard manual work (7.7 per cent), and still rarer (2.6 per cent) in peasants. Postinfarctional cardiosclerosis was also found most commonly in mental workers. In 1958 Morris and Crawford arrived at the same conclusions; in physically inactive people at the age of 45-60 stenosis of coronary arteries was encountered 50 per cent and at the age of 60-70 100 per cent more frequently than in people whose occupations involved hard manual work. A similar picture was observed in cases of postinfarction cardiosclerosis which was found three or five times as often in the former as in the latter.

Considerable differences in the extent of coronary atherosclerosis were found in the study and comparison of the coronary arteries of groups of men living in Irkutsk and in rural areas of Irkutsk Region (Vikhert and Sedov, 1969).

Above we cited data on a favourable influence of manual work on preventing coronary atherosclerosis. There are several studies, however, whose authors have not discovered any differences in IHD incidence between manual workers and people living a physically inactive life. Nicolaysen (1962) studied the incidence of primary infarction among eight occupational groups (office workers, commercial employees, transport, metallurgical, industrial and building workers) and arrived at the conclusion that the type of work, whether sedentary or involving considerable physical activity, hardly bears on the incidence of myocardial infarction. Fox and Skinner (1964) on the basis of eight years' observation in Los Angeles (Los Angeles Heart Study) mention the same incidence of new infarction cases and sudden death both among people with physically inactive occupations and those whose work involves moderate or intensive physical activity.

The results of the so-called Du Pont Study with six years of observation conducted by Pell and d'Alonzo (1963) show that manual workers are in a rather more favourable position than shop foremen, work superintendents, office workers and travelling salesmen, but in a worse position than the managerial staff of private companies, laboratory directors, etc. In the first group the annual incidence of myocardial infarction amounted tc 3.2 per 1000 observations, in the second 4, and in the third only 2.2-2.5. Villiger and Heyden (1966) conducted a retrospective analysis of physical activity of 100 patients before the myocardial infarction and of 100 control persons of a corresponding age, sex and nationality, and

found that the former had been physically much more active. If it is expressed in numbers in summer the persons of the first group were physically active 16 hours and of the second group 10, and in winter 14 and 8 hours, respectively.

Thus the findings of different researchers are quite contradictory. This is due first to the differences in the choice of the investigated groups and the criteria of physical activity, which is particularly noticeable among foreign researchers. The findings in our country are more homogeneous. Moreover, an acquaintance with them reveals quite a definite tendency, namely, the importance of the factor of nervous strain. If physical activity does play a role in itself,

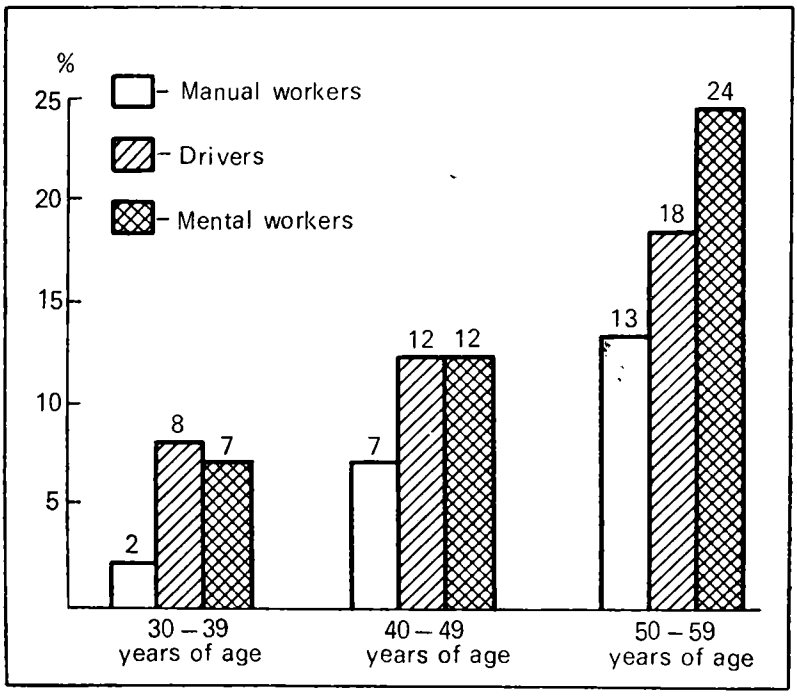

Fig. 52. Incidence of hypertension (160/95 mm Hg and higher) among mental and manual workers and drivers

it is not so great, and the neuropsychic influence that in most of the cases is connected with occupations which doom the people to a sedentary life and little physical activity is more important.

From this point of view Morris' (1960) findings may be explained by the fact that the work of bus drivers is connected not only with little physical activity, but also with much greater nervous strain than is the work of bus conductors, since driving a bus in a modern city requires continuous nervous tension and is associated with various stress factors. In this connection of some interest are the findings of Lifshits *et al.* (1969) concerning the incidence of hypertensive vascular disease and IHD among three groups of men 30-59 years of age living in Yalta.

These authors examined 353 mental workers, 319 manual workers and 375 motorcar drivers. The work of the latter on the Crimean mountain roads involves considerable neuropsychic strain. The examinations covered 77-80 per cent of people of the indicated age working in Yalta's offices and enterprises. It turned out (Fig. 52) that the incidence of arterial hypertension was the lowest among the manual workers and the highest among scientific workers and drivers. These differences were the most strongly pronounced in the younger age groups. Analogous correlations were also observed in the serum cholesterol level (Fig. 53). Electrocardiography showed

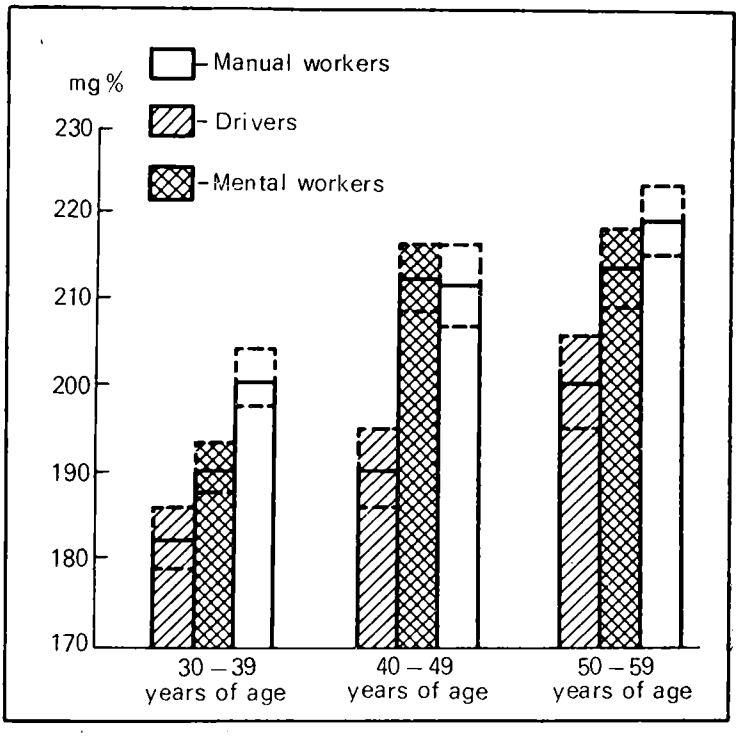

Fig. 53. Mean level of cholesterolaemia in mental and manual workers and drivers

survived myocardial infarctions at the age of 40-49 only in drivers (3.8 per cent of those examined). At the age of 50-59 its incidence among the drivers and scientific workers was the same (4.9 and 4.8 per cent, respectively), whereas the examined manual workers showed no signs of cicatricial changes in the myocardium. The latter circumstance may be due to the fact that the manual workers who had survived myocardial infarction changed their jobs.

We may also cite data on neuropsychic strain during the period preceding the development of myocardial infarction (Shkhvatsabaya, 1965).

In examining 122 patients who had survived myocardial infarction Starchevsky (1969) also found psychic overstrain in 62 per cent

of them. True, most of the patients did not indulge in sport, did not do any manual work at home and lived a sedentary life.

Daraseliya and Milorava (1969) also point out the incidence of psycho-emotional traumas as a factor conducive to the development of IHD. According to their findings, psycho-emotional trauma preceded myocardial infarction in 64 per cent of cases of office workers and in 40 per cent of cases of industrial workers.

All of the foregoing warrants the conclusion that, even though occupational physical inactivity plays a considerable role in the development of IHD, neuropsychic strain, emotional conflicts and stresses, which are much more frequently associated precisely with occupations necessarily requiring a sedentary life and thereby unfavourable combining two negative factors, are of no lesser importance.

Obesity

It may be assumed that obesity does not in itself considerably influence the development of IHD. This proposition was excellently formulated by Gofman and Young (1963), who wrote that 'overweight per se must be relatively or totally unimportant in acceleration of the process of atherosclerosis'. It is impossible clearly to distinguish the relation of excess body weight per se to the risk of developing coronary disease. Unfortunately, 'countless persons have been left with the impression that their state of overweight is of itself productive of an increased risk of development of premature atherosclerosis'. Somewhat later, while considering the relation of obesity to coronary insufficiency, Gertler *et al.* arrived at an analogous conclusion. They wrote: '...it is further emphasized that obesity was a very popular predictor at one time, but has now fallen into disuse'.

Today this question is being considered on an entirely different plane. Excess weight often correlates with an increase in the serum cholesterol and a tendency toward a rise in blood pressure. It is precisely in this respect that an increase in weight after 25 years of age is a bad prognostic sign.

Heyden (1966) examined two groups of people, one consisting of persons whose weight increased rapidly and considerably after 20-25 years of age and the other composed of persons whose weight remained stable all through life. Among the former (364 persons 30-69 years of age) there were 31 per cent hypertensives (pressure above 160/95 mm Hg) and among the latter 11 per cent (392 persons of the same age). Analogous data were obtained on hypercholesterolaemia, namely 29.5 per cent of people of the first group and only 11 per cent of the second group had serum cholesterol above 250 mg per cent. A frequent combination of elevated blood pressure with an excessive gain of weight after reaching physical maturity is also mentioned by Haulan *et al.* (1962) on the basis of 18 years of observation on 785 men (their mean age was 23.6 years in

the beginning of the study and 42 years at the end). Stamler (1963) pointed out that in men whose weight had increased 20 per cent since youth hypertension occurred 2.5 times as frequently as in those with stable weight. They also found a mean difference of 21 mg per cent in the cholesterol level of the two groups.

Apparently precisely the last two factors exert a decisive influence on the development of IHD in the obese. As a matter of fact, Schettler did not find any signs of coronary insufficiency in 45-60-year-old men with excess weight (10 kg and more) but normal blood pressure. Analogous data are cited by Spain *et al.* (1961) on the basis of a study of 5000 Israeli males of the same cultural and dietary standards. If we exclude the obese persons with hypertension (and diabetes) from this group, the incidence of IHD among the rest of them does not exceed that among the persons with normal weight.

Goldberg *et al.* (1964) also noted the absence of connection between obesity and the incidence of IHD. However, in cases of obesity combined with hypertension the incidence of IHD sharply increases; in people with normal pressure and a normal diet the incidence of IHD amounted to 21 ± 3 per cent, in obese people with normal pressure it was 27 ± 5.3 per cent, and in cases of obesity combined with hypertension 40.8 ± 2 per cent (the differences are statistically reliable between the first and third and the second and third groups).

The excess weight must be very high (30 per cent in the Framingham experiment and 40 per cent higher than the average in Albany) in order somehow to affect the IHD incidence. However, according to Kannel *et al.* (1965), the incidence of angina pectoris increases in persons whose weight is 25 per cent or more above normal.

Thus it may apparently be assumed that a considerable increase in weight (10-15 per cent and more than average after 25 years of age) is not in itself conducive to the development of coronary atherosclerosis and does not increase the probability of contracting IHD. But since excess weight is often accompanied with elevated blood pressure the resultant combination is unfavourable and may be regarded as one of the risk factors.

Other Epidemiological Factors

The Framingham study showed that non-specific small changes in the ECG are very important as a risk factor in the development of IHD. Non-specific deviations in the ECG are connected with an increased risk of developing coronary disease of the heart. Men and women with these deviations develop the disease about twice as frequently as do persons with a normal electrocardiogram (Kannel *et al.*, 1965). The minor manifestations comprise changes in the $ST-T$ interval and an isolated negative T wave. Particular importance is attached to disturbances in conduction.

Signs of left ventricular hypertrophy on the ECG are unfavourable, according to the Albany studies, they increase the IHD fourfold (according to the Framingham experiment, two-fold).

Summing up the findings of the Framingham Study Higgins *et al.* (1965) cite the following data: in cases of an isolated *Q* wave the danger of dying of IHD increases three-fold, the wider the *Q* wave the greater the danger. An isolated negative *T* wave increases the danger of contracting the disease three-fold and that of death five-fold. Various combinations of these changes increase the chances of contracting this disease two to four times and those of death four or six times.

Indications of the connection between the disturbances in carbohydrate metabolism and the development of IHD have appeared of late. Among myocardial infarction patients Reaven *et al.* (1962) found decrease in glucose tolerance in 76 per cent (as against 32 per cent in the control).

According to Pell and d'Alonzo (1963), the incidence of myocardial infarction in 25-64-year-old persons affected with diabetes mellitus is 2.5 times as high as in those of the control group. Sievers *et al.* (1961) found five times as many cases of diabetes among 1530 patients with fresh myocardial infarction as among the rest of the population. Ostrander *et al.* (1965) noted a higher incidence of various deviations in the ECG among persons with a decreased glucose tolerance.

At the same time, according to our data obtained in a study of the coronary arteries and the causes of death of persons up to 50 years of age with pure diabetes[1] (42 cases), the degree of atherosclerosis in them and the incidence of stenosis did not exceed those of practically healthy people who died of fortuitous causes connected with trauma and without signs of coronary disturbances, and were much lower than those of people of the same age who died of different manifestations of atherosclerosis. Most of the young people affected by diabetes died of causes directly connected with diabetes (coma, infections, etc.); only two of them had myocardial infarction. On the contrary, the overwhelming majority of diabetes patients at the age over 50 died of various manifestations of atherosclerosis, including myocardial infarction (72.3 per cent men and 67.1 per cent women). Coronary atherosclerosis in them was as strongly pronounced as that of the people who died of atherosclerosis, but without diabetes (Fig. 54). We believe that in young people diabetes does not in itself intensify the course of the atherosclerotic process. In elderly people it is not excluded that diabetes itself serves as a manifestation of an advanced atherosclerotic process with affection of the vessels that supply the pancreas. This explains its frequent combination with myocardial infarction which is a consequence of

[1] Pure diabetes, i.e. without hypertension, cardiac hypertrophy and other diseases which may influence the development of atherosclerosis.

coronary atherosclerosis. At any rate, the question of the connection between the disturbances in carbohydrate metabolism and IHD requires further detailed clinical and, especially, epidemiological study.

The role of heredity in the development of IHD is discussed in a number of studies. Literature contains information on a high incidence of myocardial infarction in certain families (Gertler *et al.*, 1954; Rose, 1964; Villiger and Heyden, 1966). Walker and Gregoratos (1967) interrogated 100 patients who had survived severe infarction before 40 years of age and found the disease to have been

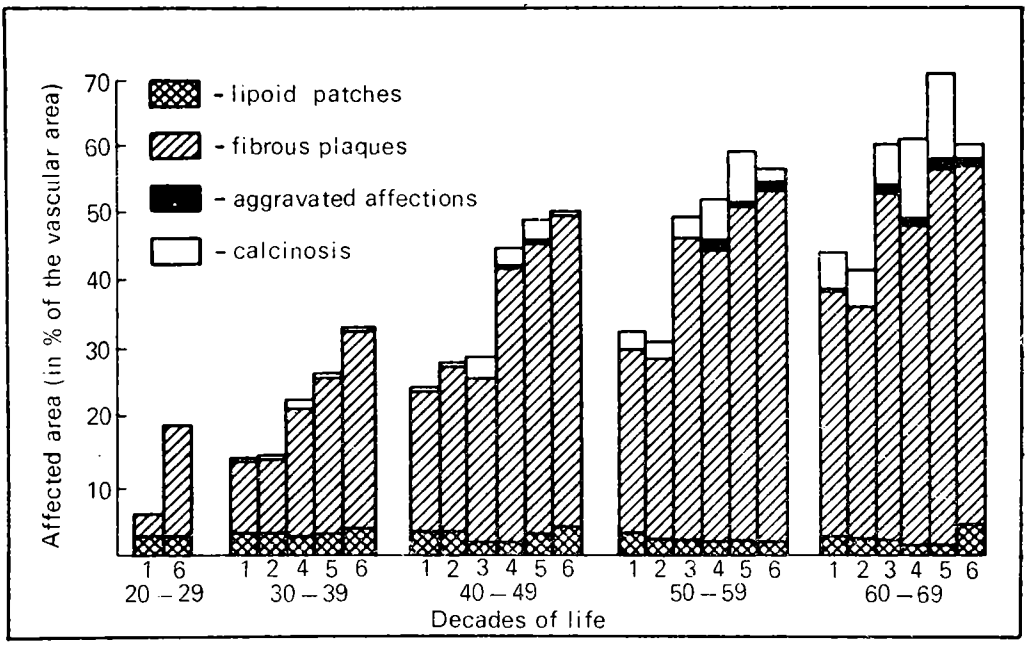

Fig. 54. Characteristics of the atherosclerotic changes in the descending branch of the left coronary artery during various diseases (in males)

1—healthy; *2*—malignant tumours; *3*—diabetes mellitus; *4*—atherosclerosis; *5*—hypertensive vascular disease; *6*—symptomatic hypertension

familial in 47 per cent of cases as against 20 per cent in the control. Similar data are cited by Heyden and Heyman (1967); of the 40 myocardial infarction patients one or both parents of 34 had died of cardiovascular diseases, as against 23 of the 40 control persons of the same age, sex and nationality.

The data in the literature do not confirm the opinion on the increasing influence of alcohol on IHD. This is indicated by the studies of Dawber *et al.* (1959) (Framingham experiment); Paul *et al.* (1963); Doyle *et al.* (1959) (epidemiological studies in Albany). Kasanen *et al.* (1963) studied the consumption of alcohol by 100 myocardial infarction patients at the age of 30-60 and compared their data with those obtained in patients hospitalized for other

causes. No differences were found. At the same time Villiger and Heyden (1966) compared 72 infarction patients with 72 healthy persons and found an essential difference; among the myocardial infarction patients there were 32 chronic alcoholics, while among the healthy persons there were only six. The authors hold, however, that these data do not prove that alcoholism is conducive to the development of IHD because, if we take not healthy people as the control, but those hospitalized for other diseases (not IHD), we shall find about as many alcoholics among them. The authors explain it by the fact that alcoholism is generally conducive to various diseases. Sedov (1969) also failed to find any intensification of coronary atherosclerosis in people who consume large quantities of alcohol.

The only study which indicates greater affection of the coronary arteries in alcoholics is that of Rapoport (1935), according to which severe forms of atherosclerosis in young people (20-40 years of age) are encountered mainly in alcoholics. Also noteworthy is the author's indication that selective affection of the coronary vessels is much more frequently observed in alcoholics.

The studies of the influence of alcohol are complicated also by the fact that the drinkers and their relatives naturally often conceal or deny their weakness, and this may misconstrue the results of the study.

Such are the brief data on the role of various factors, endogenous and exogenous, in the development of IHD. Of course, our knowledge in this field is far from complete and often quite contradictory. It may, nevertheless, be assumed that we are already in a position to foresee with a good deal of probability the development of IHD in certain groups of the population.

4

MAIN CLINICAL SYNDROMES OF ACUTE MYOCARDIAL INFARCTION

The picture of myocardial infarction aggravated by shock and rupture of the heart was first described in 1798 by K. F. Knopf, a St. Petersburg physician. At the end of the next century (1878) Hammer reported individual cases where the disease was diagnosed during life. V. M. Kernig (1892-1904) described in detail the clinical picture of pericarditis aggravating myocardial infarction and designated it by the now accepted term of pericarditis epistenocardiaca. A classical description of the clinical aspects of myocardial infarction was made by V. P. Obraztsov and N. D. Strazhesko at the First Congress of Russian Internists in 1909. But for a long time myocardial infarction continued to be rarely diagnosed and usually only in severe cases.

The introduction of the electrocardiographic method into clinical practice (Pardee, 1920; Parkinson and Bedford, 1927; Barnes, 1934, and White, 1945) and its subsequent wide use sharply changed the physicians' ideas on the character of clinical manifestations of infarction. It became evident that the changes in the ECG were not only an objective, but also a very frequent sign of this disease.

The application of chest leads into clinical practice appreciably facilitated the diagnosis not only of severe, but also of atypical forms of infarction which simulated angina pectoris, disturbances in cardiac rhythm and heart failure. Electrocardiography is still one of the principal methods which enables not only myocardial infarction, but also the conditions threatening the development of this severe disease to be diagnosed.

In the last ten or fifteen years the diagnosis of myocardial infarction became enriched with several new methods. Of the greatest

practical importance are those that make it possible to determine the changes in the activity of the enzymes of the patient's blood serum.

Myocardial infarction is a dangerous complication of chronic diseases of the coronary arteries and certain other diseases, e.g. protracted septic endocarditis. Its clinical manifestations are so varied that even the most experienced physician is not always able to make a correct diagnosis. The main reason for the diagnostic difficulties is, in our opinion, that the clinical picture of infarction does not have a single constant sign or symptom.

Although the name of the disease indicates its intimate connections with disturbance in the normal structure of the myocardium, in some cases death occurs before clinical, laboratory or morphological signs of necrosis of the heart muscle appear. The other signs and symptoms of infarction are still less constant.

Many diseases may be mentioned whose clinical manifestations at the early stages of their development extremely resemble the clinical manifestations of infarction. In these cases a correct diagnosis can be established only after long observation. The absence of constant signs complicates not only the diagnosis of infarction. It is the reason that no single principle of clinical classification of various forms of infarction has yet been elaborated.

The classical work of Obraztsov and Strazhesko *Concerning the Symptomatology and Diagnosis of Thrombosis of the Coronary Arteries* (1909) describes three clinical pictures of myocardial infarction: with characteristic pains in the region of the heart, with attacks of severe suffocation, and with a feeling of 'strong and distressing pressure in the pit of the stomach'. As the number of observations increased it became clear that the algesic, asthmatic and gastralgic forms of infarction described by Obraztsov and Strazhesko do not exhaust all the clinical manifestations of the disease.

Bukhshtab and Siterman (1938) made a detailed study of the clinical picture of myocardial infarctions with a moderate pain syndrome and designated them by the terms of 'effaced and rudimentary'. Grotel (1940) reported a myocardial infarction with a clinical syndrome of acutely developed heart failure. This form of infarction was described in greater detail by Speransky (1935); Glagolev (1937), and others. The fundamental importance of the foregoing studies is that they reported a possible development of painless necrosis of the heart muscle.

Before the appearance of these studies pain was considered a necessary sign of any form of acute heart failure. If an infarction patient did not complain of pain in the chest, physicians never failed to find the so-called equivalents of the pain syndrome in him, which was most commonly an attack of cardiac asthma. When the existence of painless forms of myocardial infarction was, at last, recognized, all forms of this disease began to be divided into typical, i.e. with pains, and atypical, i.e. without pains.

Kryukov (1949) and Zelenin (1956) suggested ascribing to atypical myocardial infarctions not only cases with a painless onset of this disease, but also its forms with unusual localization of pains. As physicians became familiar with the clinical picture of infarction, the number of its atypical forms gradually increased; afebrile (Nezlin, 1956), oedematous (Speransky, 1949), abdominal (Glazova, 1949), cerebral and apoplectiform (Bogolepov, 1949), symptomless (Fogelson, 1938) and other forms were described. Soon the necessity arose to classify its atypical forms.

Popov (1965)' suggested distinguishing infarctions with acute heart failure and atypical localization of pains. Moreover, he considered it expedient to single out cerebral (apoplectic) and gastrointestinal forms. From what has been said it follows that Popov's classification covers only a few forms of atypical myocardial infarctions. Trying to eliminate this shortcoming Tetelbaum (1960) suggested a more complete classification of infarctions.

In addition to the classical form with the pains localized in the retrosternal region he distinguishes peripheral, abdominal, cerebral, painless and combined types of myocardial infarction. Each of these types he subdivides into four or five forms differing from each other in the extent to which the various clinical signs and symptoms are marked. Some types and forms of infarction in Tetelbaum's classification are distinguished by the presence of some remarkable clinical sign (e.g. the hemiplegic form of the cerebral type), others by the absence of some symptom (e.g. the painless type), still others by the localization of an important symptom (e.g. upper vertebral and laryngopharyngeal forms).

Tetelbaum's classification embraces all the forms of myocardial infarction—typical and atypical. Its main shortcoming is that it does not have a single classification principle. Moreover, it is difficult to agree with Tetelbaum's suggestion to regard the types of myocardial infarction, which he distinguished as definite clinical entities.

Ostapyuk (1965) distinguishes six groups of atypical infarctions. The first group comprises infarction cases with temporary and mild retrosternal pains. Atypical localization of the pains is the most characteristic sign of the second group. The other groups are distinguished by their most strongly pronounced clinical syndrome in the acute period of the disease. The author distinguishes infarctions with acute cardiac or vascular insufficiency, with disturbance in cerebral circulation and with 'acute gastric symptoms'. In these cases the pains are either slight or absent. It is not difficult to see that Ostapyuk's classification has the same shortcoming as the foregoing one, i.e. the absence of a single underlying principle.

The clinical picture of myocardial infarction may be represented as a complex of symptoms and signs arising under the influence of necrosis of the heart muscle with symptoms and signs appearing as a result of coming into play of mechanisms of protective-adaptive

reactions which facilitate the existence of the organism under conditions of a reduced minute volume.

There is no doubt that in the clinic we do not see the adaptive reactions, but the signs and symptoms which develop as a result of interaction between the organism's compensatory forces and the causal factor.

To the first group of signs and symptoms we may ascribe pain, weakness, a sharp decrease in the minute volume, slowing down of the blood flow, pericardial friction murmur, myohaemoglobinaemia and myoglobinuria, changes in the ECG, increased activity of some of the blood serum enzymes and other signs of the resorption-necrotic syndrome.

The protective-adaptive reactions developing in response to the sharp decrease in the minute volume are accompanied by the appearance of such well-known clinical signs as pallor and cooling of the skin, transient increase in the secretion (and excretion in the urine) of some hormones of the cortical and medullary layers of the adrenals, etc.

The interaction between the causal factor and the protective-adaptive reactions gives rise to the third group of signs to which we must ascribe fever, increase in the number of leucocytes in the blood, accelerated ESR, changes in the composition of blood proteins, tachycardia, oliguria, and changes in arterial and venous pressure.

The foregoing symptoms and signs form characteristic clinical syndromes whose appearance warrants the physician to suspect myocardial infarction. During the initial period of the disease it is possible to distinguish the following syndromes: pain, resorptive-necrotic, abdominal, acute heart failure, shock or collapse, disturbances in the cardiac rhythm and transient disturbances in cerebral circulation.

The extensive introduction into clinical practice of instrumental and other laboratory methods of examination has resulted in the discovery of new diagnostic criteria of infarction. The use of precisely these methods of examining patients makes it possible to diagnose the so-called latent myocardial infarctions. Laboratory data make it possible, moreover, to trace the course of the infarction.

Considering the great practical importance of the data furnished by the instrumental and laboratory methods of examination to reveal the necrosis that has occurred in the heart muscle it is apparently expedient to distinguish and describe separately the biochemical and electrocardiographic signs of myocardial infarction within the limits of the resorptive-necrotic syndrome. The great diagnostic importance of the complex of non-specific signs which it is possible to reveal by studying the morphological composition of blood has long since been generally recognized.

Some of the foregoing syndromes (e.g. the pain syndrome) are encountered in myocardial infarction very often and are sometimes

so clearly marked that they automatically engross the attention of the physician and patient. Other syndromes (e.g. heart failure) occur very often, but are at times less clearly marked and therefore often remain undiscerned.

The ECG changes and feebly marked signs of the resorptive-necrotic syndrome in cases of mild and so-called latent infarction are sometimes the only or nearly the only indications of myocardial affection.

In cases of more or less severe infarction it is possible to discover simultaneously several syndromes. In these cases some one syndrome always dominates in the clinical picture of the disease. The extent and character of the therapeutic measures carried out at the patient's bedside are largely determined by the markedness and severity of the dominating syndrome. We may with good reason speak of myocardial infarctions manifested mainly by the pain or abdominal syndromes, of myocardial infarctions with syndromes of heart failure, shock, disturbance in the cardiac rhythm and transient disorders of cerebral circulation predominating in the clinical picture, and of 'latent' or symptom-deficient myocardial infarction which is displayed mainly by feebly marked signs of the resorptive syndrome.

Pre-infarction State

Myocardial infarction often occurs suddenly. According to our findings, the disease developed without any portents in 43 per cent of cases of primary infarction. In the other 57 per cent the patients had suffered from angina pectoris over a period that ranged from a few days to several years before the onset of the infarction.

In 12 per cent of patients attacks of angina pectoris appeared for the first time one or three weeks before the infarction. In all these cases the pains were localized in the precordial region. The patients usually did not complain of irradiation of the pains, but conversation with them revealed that their pains irradiated similarly to those of the patients with chronic angina pectoris. The pains were not particularly intense, but were always accompanied by a feeling of anxiety and indefinite fear. Not the pain, but the feeling that not all was well impelled the patients to take medical advice.

The period from the appearance of angina pectoris to the moment of occurrence of the infarction ranged in 30 per cent of patients from three weeks to one year. In 15 per cent primary infarction occurred in patients who had had angina pectoris for more than one year. Thus the appearance of angina pectoris preceded the onset of myocardial infarction in more than half (57 per cent) the patients examined by us. According to Lukomsky and Tareev (1957), attacks of angina pectoris before the onset of myocardial infarction were observed considerably more often (in 83 per cent of patients). When

comparing their data with ours it should be remembered that Lukomsky and Tareev's statistics included patients with both primary and recurrent myocardial infarction. In the latter angina pectoris occurs during the pre-infarction period more frequently than in primary infarction patients.

However we appraise the figures it is clear that myocardial infarction most commonly occurs in patients affected with angina pectoris. This gives rise to the problem of differentiating the usual attacks of angina pectoris from those which end in formation of an infarct.

A pre-infarction state can be diagnosed only retrospectively. By merely observing a patient with attacks of angina pectoris a physician cannot, with any degree of certainty, either predict or exclude the possibility of the development of myocardial infarction. It has been noted, however, that infarction is sometimes preceded by a change in the character of the attacks of pain. In some cases the attacks of angina pectoris not long before infarction become more frequent. Usually they are well terminated by nitroglycerin (glyceryl trinitrate), but as soon as the action of the drug ceases the pains recur. This forces the patient to take ten to twenty tablets of nitroglycerin a day, whereas not long before that he had taken only four or six. In other cases it is a change in the severity of the attack of pains that comes to the foreground. Validol (methyl valerate) and nitroglycerin prove incapable of terminating the painful sensation, although in the past they relieved it quite adequately.

In some cases not long before the onset of infarction the angina of effort was transformed into angina of rest. If formerly the retrosternal pains had developed in these patients only under the influence of physical effort or emotional stress, now before infarction they seemed to occur without any visible cause. Sometimes the attacks of angina pectoris, from which the patient suffered for a long time, completely disappear after infarction. Angina pectoris usually recurs three to six months after infarction and less frequently a few years later. Its development in these cases, like the first appearance, indicates the possibility of a fresh infarction in the near future.

The transformation of the clinical signs of angina pectoris discussed above has been explained in the last quarter of a century by an occurrence of a subintimal haemorrhage which leads to a narrowing or even occlusion of the lumen of the corresponding branch of a coronary artery. In these cases myocardial infarction may develop some time after the onset of angina pectoris under the influence of physical strain or another factor, which increase the oxygen requirement of the myocardium. Timely hospitalization and treatment of the patient in these cases may, by preventing the possibility of physical effort and emotional stress, appreciably reduce the extent of the necrosis, if not prevent myocardial infarction. A pre-infarction state may be suspected only if the foregoing symptoms are not accompanied with an elevation of temperature,

leucocytosis, accelerated ESR, increased activity of transaminases and characteristic ECG changes. The diagnostic difficulties arising in some cases are so great that the final diagnosis may sometimes be established only after a fairly long period of observation.

Pain Syndrome

In many cases pain is the clearest sign of myocardial infarction. It usually appears at the onset of the disease and, after rapidly reaching the maximal intensity, becomes its most dramatic symptom. Only in rare cases where infarction begins with an attack of cardiac asthma, a dynamic disturbance in cerebral circulation, shock or a disturbance in the cardiac rhythm is the pain syndrome insufficiently pronounced. In these cases the pains in the chest usually appear only after the termination of arrhythmia or the attack of cardiac asthma or after the patient has been brought out of the state of shock.

In one of the cases we observed the patient suddenly fainted in the street. The pains in the chest appeared about ten minutes after he had come to. One must, apparently, not deny the existence of pain in these cases of infarction, but it is clear that it was camouflaged by other, more dangerous disturbances and, therefore, was not the leading symptom of the disease.

Severe pains may begin at any time of the day, but they most commonly occur, as was shown by Baubine (1964), at the early morning hours. They are usually accompanied by perspiration and not infrequently also by a vomiting.

In the beginning of the attack the patient is restless. Many patients experience fear of impending death. Trying to mitigate the pain they often change their position in bed or walk about the room and vainly try various methods of relieving the feeling of constriction in the chest. At the height of a not very severe attack the patient usually lies in bed, impatiently changes his positions and complains of pain. The excitement often lasts several hours and ends by the appearance of a feeling of extreme weakness and collapse.

The literary data on the incidence of the pain syndrome in myocardial infarction are quite contradictory. According to Gulo (1965), pain accompanies the development of infarction in about 70 per cent of cases and according to Baubine (1964) in 80 per cent. Sigler (1954), Lukomsky and Tareev (1958) noted that pain was the initial symptom of infarction in 95.6 per cent of hospitalized patients. The same incidence of pain in infarction is reported by Wright *et al.* (1954). Gertsen (1966) noted pain sensations only in 74.6 per cent of infarction cases. These data on the incidence of the pain syndrome in myocardial infarction should, apparently, be regarded as reduced because more than two-thirds of the patients he observed were exa-

mined in different, sometimes long, periods after the onset of the disease, when many of them were no longer able to recall in detail their sensations during its acute period.

By insistently questioning the patients on their pain sensations in the region of the heart Smetnev (1966) revealed a more or less strong pain syndrome in the beginning of infarction in 97.5 per cent of cases. In appraising these data it should be remembered that Smetnev went in an ambulance to the patients whom he already suspected of having a myocardial infarction. In the clinic he also observed and examined patients admitted with a suspicion of myocardial infarction. Such indefinite sensations as a difficulty in breathing, a mild burning or pressure behind the sternum and even a mere sensation of 'uneasiness' were recorded by him (and quite justly) as manifestations of the pain syndrome.

While working in the admission department of a multiprofile hospital, we were repeatedly convinced of the difficulty of diagnostically appraising these, at times very indefinite, sensations. Their final importance was often elucidated only retrospectively, sometimes after electrocardiography and even after some observation of the course of the disease. A carefully collected anamnesis undoubtedly helps revealing the patient's certain unpleasant sensations in the region of the heart, but in addition to this it is necessary to decide the question of their diagnostic value.

Guided by the aforesaid we evaluated retrospectively the results of personal examination of 250 myocardial infarction patients. Pain sensations in the region of the thorax on the first day of the disease were revealed in 89.6 per cent of cases. They were totally absent in 12 (4.8 per cent) patients. Unpleasant sensations in the chest in 14 (5.6 per cent) patients were of such an indefinite character that they could not in themselves be used as a symptom supporting the diagnosis of myocardial infarction.

The insufficiently pronounced pain syndrome is accounted for either by the very rapid and complete necrosis of the entire ischaemic part of the myocardium or by the patient's particularly serious condition which is observed, for example, in shock. The incidence of pain is definitely dependent on the patient's age. According to Wright *et al.* (1954), pain was the initial symptom of infarction in 96 per cent of all the patients they had examined. In patients at the age over 70 pain was noted only in 90 per cent of cases.

Of the 250 patients whom we personally examined the pain syndrome was marked in 93.6 per cent of persons under 60 and in 82.7 per cent over 60 years of age. Statistical treatment of the resultant data warrants the assertion that the difference between the compared groups is not accidental. Meerzon (1958) also points out that in elderly people pains are encountered rather less frequently and less strongly pronounced than in young people.

In recurrent myocardial infarction the pain syndrome is encountered almost as frequently as in primary infarction. According

to Popov (1964), recurrent infarction without pain was observed only in 17.2 per cent of cases.

The foregoing data show that pain is not always the first symptom of infarction. The pain syndrome is encountered at least in 70-96 per cent of cases. Its appearance in the initial period of the disease is so natural that painless infarctions are regarded as an exception to the rule. It should be remembered, however, that this exception occurs nearly in one-third of cases. The absence of pain, apparently, does not exclude, but only renders difficult the correct diagnosis of myocardial infarction.

The pains are most commonly of a pressing and constricting nature. Smarting, cutting and tearing pains occur much less frequently. In most cases in the very beginning of the disease they are not very intense. The first attack is usually followed by a temporary relief after which the attack is resumed. This time the pains are more intense than before and are accompanied with more extensive irradiation. They grow stronger with each attack and reach maximum intensity in about half an hour, the patient simultaneously sinking into extreme weakness.

Alternately intensifying and abating the pain persists for several hours or a day. Subsequently, in favourable cases, the intervals between attacks gradually begin to increase and the intensity of the pain to diminish. Sometimes the pains become unbearable from the very onset of the disease. Even intravenous injections of morphine offer only a certain relief. In such cases myocardial infarction soon usually becomes aggravated by shock.

At the onset of infarction the pains may resemble those of angina pectoris. Only a carefully collected anamnesis makes it possible to reveal the sign characteristic of infarction—the appearance of a pain syndrome without any visible cause. Sometimes it is possible to discover a more extensive irradiation of pains than in usual attacks of angina pectoris and an insufficient effectiveness of nitroglycerin (glycerin trinitrate). This type of pains is most commonly encountered in focal, usually subendocardial and intramural myocardial infarctions. These pains can be distinguished from severe attacks of angina pectoris only after fairly long observation of the patient. Of considerable help in such cases are the results of repeated clinical and laboratory tests, especially the character of the eventually occurring ECG changes.

Pain is almost always localized in the precardial region. As a rule it is of a diffuse character, but the patient usually localizes it behind the sternum. Other localizations are encountered less frequently. As in angina pectoris pain in myocardial infarction often irradiates to the shoulders, upper extremities, the neck, lower jaw and interscapular space. Mintz and Katz (1947) point out that pain only in the shoulder or only in the arm occurs extremely rarely. According to Tetelbaum (1950), in the initial stage of myocardial infarction pain is localized in 25 per cent of cases in the neck, left

arm, left scapula or upper part of the thorax and only later shifts to the region of the heart.

Irradiation of pains to the upper half of the abdomen and the epigastric region (status gastralgicus) is observed comparatively seldom. The appearance of pain in the upper part of the abdomen is usually explained by the spread of pain impulses to the neighbouring segments of the spinal cord. Tareev (1951) holds that such a localization of the pain sensations combined with cardiac fibrillation is most likely an indication of the appearance of pericarditis. The gastralgic form of infarction is encountered in 5 per cent of cases (Tetelbaum, 1960), in 3.2 per cent (Ostapyuk, 1965), and in 5.9 per cent (Gulo, 1965). In the materials collected by us the gastralgic form of myocardial infarction occurred only in 2.7 per cent of cases. It should be noted that, when these patients are questioned in detail, it is usually possible to reveal pains in the precardial region simultaneously with pains in the abdomen.

Appraising the prognostic value of pains in myocardial infarction Lukomsky and Tareev (1958) concluded that mortality is less in transitory attacks of angina pectoris (lasting up to one hour). Longer duration of attacks of pain was accompanied with an appreciable increase in mortality. Although Gulo did not note any clear parallelism between the duration of the attack of pain and mortality, he nevertheless pointed out that there were fewer fatal outcomes among patients with a shorter pain syndrome.

Pains in the precardial region are most commonly observed in infarction of the anterior and anterolateral walls of the left ventricle. Irradiation of pain to the epigastric region occurs rather more frequently in infarction of the posterior and posterolateral walls of the left ventricle. The irradiation of pain and the localization of necrosis do not correlate with each other. Localization of pain cannot be used for topical diagnosis of infarction.

In summing up the foregoing data it may be said that pain sensations are the most common symptom of myocardial infarction. They are found in not less than 70 per cent of patients. It must be especially emphasized that pain is the most common, but not always the first symptom of infarction. Its intensity and duration indicate the severity of the patient's condition at the moment of examination. A prognostic appraisal of the pain syndrome must be made with caution because the patient's fate is determined not so much by the vividness of the pain syndrome, as by the localization of the infarction, its extent and the severity of the developing disturbances in circulatory function.

The diagnostic importance of the pain syndrome is appreciably enhanced when its appearance is accompanied with changes in the character of the heart sounds. A weakening of the first heart sound is most commonly noted during the acute period of the infarction. Its sonorousness at the apex decreases to that of the second sound; it may even be weaker than the second sound. Sometimes a sharp

weakening of both heart sounds is noted. In rare cases the heart sounds remain clear in the beginning of infarction. A presystolic gallop rhythm is auscultated in about one-third of patients during the first days of infarction. A protodiastolic gallop rhythm is encountered much less frequently. Sometimes the third and fourth additional sounds merge and a summational gallop develops. The appearance of the aforesaid signs distinguishes the pain syndrome in myocardial infarction from the pain syndrome of another origin.

The pericardial friction murmur in a patient who had an attack of severe pains in the retrosternal region is of considerable diagnostic importance. It is difficult to establish the true incidence of this sign of myocardial infarction, on the one hand, because of its transient existence in most cases, and the unfavourable conditions of auscultating pericarditis located on the posterior wall of the left ventricle of the heart, on the other.

In most cases of myocardial infarction the pain syndrome is accompanied with an acceleration of the pulse to 100-120 per minute. Tachycardia in the initial period of the disease is observed on a background of normal body temperature. It must be remembered, however, that the pulse rate in myocardial infarction may be normal or even slow. The latter is usually observed in conduction disturbances and in transverse heart block.

In myocardial infarction arterial pressure usually falls. Its transitory elevation is sometimes observed only in the very beginning of the disease. The systolic arterial pressure falls particularly sharply. The diastolic pressure falls to a lesser extent. In some cases the arterial pressure falls rapidly and reaches its minimum one or two hours after the onset of the disease; in other cases it falls slowly. Its lowest level is noted only on the third or fourth day of the disease. In cases of mild infarction the arterial pressure may remain normal.

The arterial pressure that fell during the acute period gradually rises, usually in the second and rarely in the third week of the disease. During the period of convalescence the arterial pressure in most cases remains rather lower than it was before the disease. Sidorovich (1961) has shown that in patients with renal arteriosclerosis the arterial pressure may be elevated during both the acute period of infarction and in the period of convalescence. Pain syndromes of another origin are usually combined with tachycardia. In these cases the arterial pressure sharply falls only in the event of the development of a clinical picture of shock.

In most cases the pain syndrome is the first syndrome that suggests myocardial infarction. Its diagnostic importance sharply rises upon appearance of other signs of this disease. But even with the typical pain syndrome the diagnosis may be made with certainty only upon simultaneous appearance of other syndromes which are characteristic of myocardial infarction.

Resorptive-necrotic Syndrome

The decomposition of muscle fibres and absorption of the products of autolytic splitting of protein substances lead, on the one hand, to auto-immunization of the organism, the clearest manifestation of which is, apparently, the postinfarction syndrome, and, on the other hand, to the development of a series of general reactions manifested in fever, changes in the blood morphological picture and acceleration of ESR. The necrosis of the heart muscle is but the cause of these changes. The degree of their manifestation is determined not only by the extent of the necrosis and the rate of resorption of the necrotic material, but also by the organism's reactivity. The manifestation of leucocytosis in experimental coronary failure depends on nervous and endocrine factors.

At the onset of the disease the body temperature remains normal. Febrile reaction most commonly appears on the second or third day. In moderate cases the temperature rises to 37-38 °C and persists at this level for three or four days. High fever may also last longer, e.g. for two weeks. We found complications in all cases of infarction with fever lasting more than a week. Prolonged fever most commonly proved to be one of the manifestations of pneumonia or pulmonary infarction.

Febrile reaction was observed by Lukomsky and Tareev (1958) in 81.4 per cent of myocardial infarction patients, and by Wright *et al.* (1954) in 91 per cent. We found an elevated body temperature at the onset of the disease in 76.5 per cent of patients. Febrile reaction was absent particularly often in old people with a microfocal recurrent myocardial infarction and in patients in a state of shock.

Febrile reaction is one of the important diagnostic signs of infarction. Its appearance after one or several attacks of pain in the chest makes it possible in many cases to distinguish myocardial infarction from angina pectoris. It should be kept in mind, however, that fever is a non-specific organism's reaction to the action of many pathogenic factors and that it acquires a certain diagnostic importance only in context with clinical manifestations of the disease. Neither the presence nor the absence of the febrile reaction in itself offers any grounds for diagnosing or excluding myocardial infarction. In other words, diagnostic importance should be attached to the fever itself, but still more to the background on which it appears.

Several days after the onset of infarction the temperature usually returns to normal. Prolonged subfebrile temperature indicates the appearance of complications: thromboendocarditis and a postinfarction syndrome. A periodic rise in temperature often shows the formation of fresh necroses in the myocardium. While we do not subscribe to the views of the reflex origin of fever in myocardial infarction, we fully agree with the clinicians who hold that the time of its appearance is of a considerable diagnostic importance and its

duration may be used as a criterion which makes it possible to watch the course of the disease.

Aseptic inflammation of the myocardium during its infarction is accompanied not only by a febrile reaction, but also by leucocytosis. In myocardial infarction the number of leucocytes is in most cases increased, and only in 10-11 per cent of patients remains normal during its course. Leucocytosis sometimes appears during the very first hours of the disease. According to Lukomsky and Tareev (1958), leucocytosis is observed on the first day of the disease in almost one-third of patients, and during the first three days in nearly 70 per cent. We observed it in 85 per cent of patients. It is assumed that the intensity of leucocytosis is determined by the extent of the infarction and is therefore of prognostic importance. Many authors point out both the correctness and groundlessness of the aforesaid proposition, but everybody agrees that leucocytosis above 20 000 is an unfavourable prognostic sign.

In some cases the number of leucocytes returns to normal in a few days, in others in several months. A prolonged leucocytosis or its wavelike rises and falls are observed, like persistent fever, in the development of complications. The number of leucocytes in the blood increases mainly through an increase in the number of neutrophils.

In the first days of the disease the number of eosinophils sharply decreases. Aneosinophilia often develops. Later the number of eosinophils in the blood appreciably increases and sometimes exceeds the normal level. We cannot confirm the opinion of some authors on the considerable prognostic value of leucocytosis or of the changes in the leucocyte formula of the blood. This index, like the others, should be appraised only in connection with the total clinical picture of the disease.

According to Loginov (1961) and Zolotova-Kostomarova (1961), the erythrocyte number appreciably increases in myocardial infarction from the first days of the disease. The haemoglobin content in myocardial infarction patients somewhat increases, which may be associated with the developing haemoconcentration. This is one of the causes of thrombus formation.

In the first days of infarction the ESR may remain normal despite the leucocytosis and fever. Acceleration of the ESR begins in most cases one or two days after the onset of fever and appearance of leucocytosis, the ESR remaining accelerated until the infarction is completely healed. Considerable diagnostic importance is usually attached to the acceleration of the ESR. The dynamics of the ESR, like that of leucocytosis, makes it possible to watch the course of the disease. We are not inclined to overestimate this index because we were unable to note any parallelism between mortality from myocardial infarction and the degree of the ESR acceleration.

The concentration of enzymes is much higher in the myocardium than in the blood serum. According to Lysenko (1966) and other

authors, the development of an infarction leads after the very first 12-24 hours to an almost total cessation of the enzymatic activity in the affected parts of the heart muscle. At the same time the activity of some enzymes in blood serum considerably increases. Comparison of the aforesaid facts suggests that in myocardial infarction the enzymatic activity of the blood increases through migration of the enzymes from the necrotized muscle cells.

The 'necrotic' theory of hyperenzymaemia was particularly convincingly confirmed in observations of the changes in the activity of creatinine phosphokinase and lactic dehydrogenase. The concentration of creatinine phosphokinase in the myocardium and skeletal muscles is about 20 times as high as it is in other organs. Its activity in the serum of the myocardial infarction patient increases most likely through migration of the enzyme from the necrotized cells of the heart muscle.

Some enzymes can be divided into fractions which differ from each other in the rate of migration in the electric field. The lactic dehydrogenase of the human serum is divided electrophoretically into five fractions usually called iso-enzymes, namely, LDH_1, LDH_2, LDH_3, LDH_4 and LDH_5. The heart muscle contains mainly the most rapidly migrating fractions LDH_1 and LDH_2, while the liver contains the slowly migrating fractions LDH_4 and LDH_5. It appeared that the LDH_1 and LDH_2 activity in the blood serum sharply increases in myocardial infarction, whereas diseases of the liver are mainly accompanied with an increase in LDH_5 activity. The iso-enzyme composition of the serum is in some measure determined by the iso-enzyme composition of the affected organ. The increase in LDH_1 and LDH_2 is apparently due to the specificity of the iso-enzyme composition of the heart muscle.

The migration of the enzymes from the necrotized cells is apparently but one of the causes of hyperenzymaemia. In the blood serum not all enzymes, but only some of those contained in the myocardium, become more active. In myocardial infarction the activity of individual enzymes, e.g. pseudocholinesterase, even decreases.

The activity of some enzymes in the blood serum of myocardial infarction patients sometimes considerably exceeds their total activity in the heart. This paradox is not difficult to understand, if we assume that the enzymes enter the blood serum from the myocardium, as well as from other organs. Necrosis is apparently only one of the reasons for their increased migration from the cell, which may also lose its enzymes in metabolic disturbances developing under the influence of hypoxia and changes in the functional state of the endocrine organs and the central nervous system.

In 1954 La Due, Wroblewski and Karmen suggested the use of hyperenzymaemia in diagnosing myocardial infarction. Considerable factual material on using enzymatic tests in the clinic has now been accumulated. For diagnostic purposes it is recommended to determine the enzymes whose activity in myocardial infarction

regularly and sharply increases. These enzymes comprise aspartic transaminase, lactic dehydrogenase, aldolase, alanine aminotranspherase, creatinine phosphokinase and DNAse.

Aspartic transaminase catalyses the transfer of the amino group from glutamic acid to oxalo-acetic acid. As a result of this transamination reaction, which occurs only in the presence of phosphopyridoxal, aspartic and d-ketoglutaric acids are formed. Aspartic aminotranspherase is widely distributed in various human tissues. Considerable amounts of it are also contained in the heart and skeletal muscles, the liver, brain, kidneys, spleen and pancreas.

The activity of aspartic aminotranspherase in the serum of healthy man (determined colorimetrically) ranges from 8 to 40 units. Shelagurov and Trushinsky (1963) collected data on 3665 myocardial infarctions. In 96.7 per cent of cases the activity of aspartic aminotranspherase increased more than 50 per cent. Its maximum activity is observed at the end of the first and on the second day of the disease. In cases of uncomplicated infarction its activity returns to normal between the third and seventh days of the disease.

The duration of hyperenzymaemia does not depend on the extent of myocardial infarction. It is determined by the time of the onset and the character of complications added to the main disease. The onset of a recurrent infarction is accompanied with a new increase in the activity of the enzyme, therefore dynamic observation of its level in the blood serum makes it possible to obtain very valuable data on the course of the disease.

The activity of aspartic transaminase in experimental myocardial infarction increases parallel with the extent of the infarction (Korovkin, 1965). The results of clinical and laboratory comparisons do not confirm this regularity. According to clinicians, the activity of aspartic aminotranspherase sometimes remains unchanged in patients with an incontestable myocardial infarction or markedly increases in patients without any foci of necrosis in the heart muscle.

The aspartic aminotranspherase activity in microfocal myocardial infarction may not go beyond normal. Nekrasova (1962) links the maintenance of normal activity of this enzyme in the serum of myocardial infarction patients either with its diminished content in the myocardium of atherosclerotic cardiosclerosis patients or with a decrease in its activity owing to a deficiency of phosphopyridoxal. The decrease in the activity of transaminases found by the author in experimental atherosclerosis is probably an adequate substantiation of the foregoing hypothesis.

Aspartic aminotranspherase is found not only in the heart, but also in many other organs. Acute diseases of the liver (hepatitis), skeletal muscles (dermatomyositis), kidneys (infarctions), brain (apoplexy), pancreas (acute cholecystopancreatitis) and myocarditis involve, like myocardial infarction, a rise in the level of aspartic aminotranspherase in the blood serum.

The increase in the activity of this enzyme may be ascribed to acute necrosis in the myocardium only in cases where it is possible reliably to exclude all the foregoing diseases. Moreover, it should be taken into account that the activity of aspartic aminotranspherase noticeably increases after administration of morphine and its substitutes, some anticoagulants (Nekrasova, 1962), and also in paroxysmal tachycardia and other serious arrhythmias (Melkumova, 1961), severe acute and chronic heart failure, pulmonary infarction (Denney *et al.*, 1959, and Brereton *et al.*, 1965), exudative pericarditis and, possibly, the postinfarction syndrome (Nekrasova, 1962).

High activity of aspartic aminotranspherase is encountered in most cases of myocardial infarction. And, although, this test is non-specific, it may be useful when myocardial infarction is suspected in a patient with a block of one of the branches of the bundle of His, the Wolff-Parkinson-White syndrome or an ECG changed because of former infarctions.

The diagnostic value of the test noticeably increases when repeated on the same patient because myocardial infarction is characterized not only by an increase in the activity of aspartic aminotranspherase, but also by certain dynamics of this activity in time. To reveal it it takes time the duration of which may noticeably vary in individual cases. Sometimes the physician must draw a final conclusion on the character of the disease before receiving the results of dynamic determination of the aspartic aminotranspherase activity or the dynamic ECG changes, but the lack of time is no reason for denying the differential-diagnostic value of these tests.

Lactic dehydrogenase catalyses the oxidation of l-lactate to pyruvic acid. It is found in all organs and tissues. Its greatest activity has been found in the kidneys, striated muscles, liver, pancreas and spleen. According to combined statistics of Shelagurov and Trushinsky (1965), myocardial infarction is accompanied with a heightening activity of lactic dehydrogenase in 93 per cent of cases. Its activivity in the blood serum begins to increase about six to eight hours after the onset of infarction and reaches its maximum in one or two days.

A characteristic feature of lactic dehydrogenase is that its increased activity persists for two or three weeks of the disease (Tamarkina, 1965). In that respect it differs favourably from aspartic aminotranspherase the increased activity of which returns to normal much sooner. The content of lactic dehydrogenase in the blood increases not only in myocardial infarction, but also in diseases of the liver and kidneys, and in all illnesses attended with haemolysis of erythrocytes, and in leucoses, lymphogranulomatosis and other tumours.

As was already noted, lactic dehydrogenase is present in the blood serum in five molecular forms which can be separated from each other by electrophoresis on starch gel (Chazov *et al.*, 1966).

After myocardial infarction the content of LDH_1 and LDH_2 (iso-

enzymes of the heart muscle) sharply increases, whereas affections of the liver are accompanied with an increased activity of LDH_5 (iso-enzyme of hepatic tissue). In myocardial infarction the iso-enzyme activity of the heart muscle persists much longer, than the total activity of lactic dehydrogenase, and what is particularly important it noticeably increases also in subendocardial myocardial infarctions in which the activity of other enzymes usually does not change.

By determining the activity of LDH in polyacryl blocks Chazov *et al.* (1966) found that the LDH_2/LDH_1 ratio amounting to 1.15 in healthy man decreases to 1.0 in the myocardial infarction patient. Thromboembolism of the pulmonary artery is accompanied with a simultaneous rise in the activity of LDH_2, LDH_3 and LDH_4 fractions. The degree of the increase in the activity of these fractions in the blood serum is proportional to the extent of the pulmonary infarction.

In appraising the results of this test it should be kept in mind that it is just as non-specific as the tests for revealing the increased activity of other blood serum enzymes. The activity of the iso-enzymes of the heart muscle (LDH_1) often increases in thyrotoxicosis, cancer of the stomach, renal infarction, pernicious anaemia and certain other diseases.

Alanine aminotranspherase catalyses the transfer of the amino group from glutamic to pyruvic acid. It is found in large amounts in the liver, pancreas, heart and skeletal muscles. Its activity increases only in extensive myocardial infarctions, but not sharply and not for long. The test is positive only in 64.3 per cent of the cases.

Nekrasova (1962) found that in myocardial infarction the activity of alanine aminotranspherase changes parallel with the extent of the necroses in the liver. If necroses of separate groups of hepatic cells were found in severe myocardial infarction, the alanine aminotranspherase activity was increased to 60-80 units. In the development of centrilobular necroses it increased to 240 units, indicating indirectly that the increase in its activity in severe myocardial infarction is apparently mainly of a hepatic origin.

It is also well known that the alanine aminotranspherase activity changes in other liver diseases. It sharply increases already in the incubation period of infectious hepatitis and persists at a higher level for two or three weeks.

Aldolase is a very widespread enzyme and is found in considerable amounts in the heart, skeletal muscles and the liver. In myocardial infarction its increased content is noted in 89.1 per cent of cases. The activity of this enzyme, like that of alanine aminotranspherase sharply changes in diseases of the liver. Thus the diagnostic value of this enzyme is not particularly high. The aldolase activity in the blood reaches its maximum on the second day and persists at a high level until the seventh or eighth day of the disease.

The increase in its activity is determined mainly by the extent of the inflammatory processes in various organs and not by that of the myocardial infarction.

Creatinine phosphokinase catalyses the transfer of the phosphate group from the adenosine triphosphoric acid to creatine with adenosine diphosphate and creatine phosphate forming as a result.

By employing the spectrophotometric method of determining creatinine phosphokinase Stepanian *et al.* (1964) and Preston *et al.* (1965) found that its content in the serum varies from 0.35 to 4 u/ml. It enters the serum from muscular and probably cerebral tissue.

Creatinine phosphokinase activity in a myocardial infarction patient begins to increase three or four hours after a pain attack and in 10-12 hours exceeds the initial level usually at least threefold. In myocardial infarction creatinine phosphokinase content in the blood often increases 20-30 times. This noticeably helps to distinguish the positive test from the negative or doubtful one. Its content in the blood returns to normal 48-72 hours after the onset of the disease.

This shortcoming is apparently one of the reasons that Tamarkina (1965) found an increased activity of creatinine phosphokinase in only 78.7 per cent of myocardial infarction patients.

The foregoing enzymes enter the blood because of an impaired permeability of the cell membranes. Their content in the blood appreciably increases in more or less marked myocardial ischaemia of any origin. This shortcoming seems to have been eliminated in the diagnostic test suggested by Lysenko (1966) who determined the blood content of desoxyribonucleic acid decomposition products which enter the circulation as a result of destruction of the cell nuclei, i.e. only when ischaemia of the myocardium is completed by disintegration of its cell structures.

The content of acid-soluble decomposition products of desoxyribonucleic acid (desoxyribose derivatives) in the blood serum of healthy men is 12-18 mg per cent. The onset of myocardial infarction is accompanied with a nearly 2-4-fold increase in their concentration, i.e. to 20-50 mg per cent. The increased content of desoxyribose derivatives in the blood serum of myocardial infarction patients is found during the whole acute period because in the myocardium the nuclei of the muscle cells are first disintegrated, and then the nuclei of leucocytes penetrating to the necrotic zone and the nuclei of the cells of the inflammatory infiltrate. The onset of a recurrent myocardial infarction involves a recurrent increase in the content of acid-soluble desoxyribose derivatives in the blood serum.

This test, as well as others, is non-specific. The content of desoxyribose derivatives in the blood serum noticeably increases not only in myocardial infarction, but also in any destructive process irrespective of its localization and cause. An increase in their content is noted in leucoses, collagenoses and most inflammatory dis-

eases of any aetiology, for which reason an increase in decomposition products of desoxyribonucleic acid in the blood serum acquires diagnostic importance only in connection with the total clinical picture of the disease.

The enzymatic tests enumerated above are widely used in the clinic in diagnosing myocardial infarction and in most cases they yield positive results. This makes it possible to regard them as auxiliary diagnostic tests the negative results of which do not exclude the diagnosis of myocardial infarction and the positive results do not always confirm its presence.

Myocardial infarction is most commonly accompanied with an increased activity of aspartic aminotranspherase, but its content in the blood changes in myocardial infarction as in many other diseases. The changes in the activity of the other enzymes proved even less specific than those of aspartic transaminase.

To surmount this difficulty it is being recommended of late to determine the activity of several enzymes simultaneously, i.e. to use for diagnostic purposes a 'battery of enzymes' apparently in the hope that the shortcomings of one will be balanced by the merits of another. The diagnostic value of various combinations of enzyme tests has now been tested. The activity of the following combinations of enzymes was determined: aspartic aminotranspherase, glutamine pyruvic transaminase, aldolase (Nekrasova, 1962), lactic dehydrogenase and creatinine phosphokinase (Gracheva and Ivanova, 1969), creatinine phosphokinase, aspartic aminotranspherase, lactic dehydrogenase, glutamine pyruvic transaminase (Tamarkina, 1965) and several others. The diagnostic value of these 'enzyme batteries' did not prove convincingly superior to that of any single test.

The ECG signs of the resorptive syndrome are described in a separate chapter because of the particular importance of the results obtained and the difficulties of their interpretation.

Myocardial infarction appearing in a part that has no collateral blood supply sometimes occurs so rapidly that there are no sensations of pain. If it is of a small size, its necrosis may not involve any noticeable disturbances in the function of the cardiovascular system. In these cases myocardial infarction is latent and is sometimes characterized only by signs arising as a result of resorption of the decomposition products of the heart muscle. Since necrosis of the heart muscle is observed in every case of infarction signs of resorption of morphological heart structures must also be found in every case.

The diagnostic value of the resorptive syndrome is determined by the fact that it is the most constant sign of myocardial infarction, and is found practically in every postmortem examination. Without revealment of its signs (fever, leucocytosis, accelerated ESR, increased activity of the enzyme, ECG changes, etc.) the diagnosis of myocardial infarction cannot now be considered adequately substantiated.

Acute Heart Failure

Numerous experimental studies carried out in many countries employing various methods have convincingly shown that occlusion of a coronary artery always results in an inability of the heart to maintain the minute volume at a level adequate to the venous influx. In each experiment the occlusion of the left coronary artery caused failure of the left ventricle, and occlusion of the right coronary artery failure of the right ventricle. The disturbances in haemodynamics lead to a rise in diastolic pressure in the corresponding ventricle and in the blood pressure in the atria and the veins which empty into them. In occlusion of the main trunk of the left coronary artery the pressure also increases in the pulmonary artery.

In man myocardial infarction most commonly develops as a result of occlusion of branches of the left coronary artery. Considering the experimental data it should be expected that each case of this disease would be accompanied with signs of acute left ventricular failure. Clinical experience clearly contradicts this proposition. Myocardial infarction sometimes occurs without any marked disturbances in circulation and sometimes even without any symptoms. Acute circulatory failure in myocardial infarction may occur with a clinical picture of disturbances in cerebral circulation, collapse or shock.

The true incidence of left ventricular failure in myocardial infarction is still unknown. According to Gelshtein (1951), cardiac failure during the acute period is an unusual phenomenon even in extensive infarctions. Rosenbaum and Levine (1946) also point out that acute left ventricular failure in the beginning of infarction is encountered quite infrequently. Yater *et al.* (1948) observed it in only 2 per cent of patients.

Of late this complication began to arise rather more often. Teodori (1953) diagnosed acute heart failure in 36.6 per cent of all myocardial infarction cases, and Matusova (1964) congestive heart failure 'mainly of a left ventricular type' in 48.8 per cent of cases. According to Glazova (1956), signs of cardiac failure can be revealed in 85.8 per cent of myocardial infarction patients.

The foregoing data leave no doubt that not every case of myocardial infarction involves acute failure of the left ventricle. The reasons for the divergence between the data of experiment and clinical observations of patients are apparently the enormous reserve of the contractile function of the myocardium and the difficulties of clinically diagnosing feebly marked left ventricular failure.

Gvatua (1957), Mdinaradze (1966), and others found that in many cases of myocardial infarction the minute volume and the systolic ejection are maintained at a normal level. The method of continuous recording of haemodynamic indices enabled us to discover that after occlusion of the left coronary artery the minute volume may sometimes for a short period even exceed its value observed

during the initial period. The compensation of blood circulation noted in these experiments apparently takes place through hyperfunction of those parts of the myocardium, which remain unaffected.

Meerson (1960) studied in detail the dynamics of the biochemical processes coming into play in the myocardium during its compensatory hypertrophy. He found that the healthy parts of the heart are at first in a state of acute overstrain that gives rise to a sharp increase in the activity of the oxidation-reduction enzyme systems of the myocardium in the cells of which an intensive synthesis of proteins develops. The end result of these processes is a certain increase in the contractile function of the healthy parts of the myocardium. The foregoing results of clinical observations and experimental studies leave no doubt that this mechanism is highly effective. Its activity prevents the minute volume from falling and sometimes makes it possible to maintain it at the normal level.

In a healthy heart the influx of blood to the ventricle equals systolic ejection from it. The increase in the speed of the venous influx is always accompanied with an adequate increase in the systolic ejection. The blood pressure in the atrium of a healthy heart is always normal. Blood pressure before the ventricle rises only in cases when, because of its diminished contractility, the ventricle proves unable to increase the systolic ejection to the amount that equals the venous influx. The increase in blood pressure before the ventricle is one of the earliest haemodynamic signs of failure of the contractile function of the ventricle.

In myocardial infarction the blood pressure in the left atrium is always noticeably raised. At the same time the speed of blood influx to the ventricle also rises. The increase in the venous influx is, as is known, one of the reasons for the increased contractile function of the myocardium and, consequently, for maintaining the minute volume at the normal level.

The rise in pressure in the left ventricle and left atrium also causes its increase in the pulmonary veins and capillaries. The amount of blood in the lungs markedly increases, which inevitably involves decreased elasticity and expansibility of the pulmonary tissue during inhalations and exhalations. The respiration grows shallow. The decrease in the depth of respiration always threatens an oxygen hunger. Homeostasis of the oxygen content in the arterial blood is achieved through the development of compensatory tachypnoea.

Thus the increase in the venous and capillary pressure in the lungs is the first reason for dyspnoea in the patient with an infarction of the left ventricle. It is also necessary to note that the pressure in the pulmonary vessels in acute left ventricular failure also increases as a result of an addition of pulmonary vasoconstriction (Kitayev's reflex) to the aforesaid retrograde congestion.

In healthy man the pressure in pulmonary capillaries does not exceed 10 mm Hg. It is much lower than the colloid-osmotic pressure of the plasma, as a result of which the fluid introduced into the

alveoli always shifts to the pulmonary capillaries. In myocardial infarction the acute left ventricular failure is accompanied with a rise in pressure in the pulmonary capillaries. When the blood pressure in the pulmonary capillaries exceeds the critical level, i.e. the colloid-osmotic pressure of the plasma, the fluid begins to shift from the capillaries to the alveoli, and a clinical picture of pulmonary oedema develops.

In cases of more severe left ventricular insufficiency the patient develops orthopnoea which, like dyspnoea, arises as a result of pulmonary hyperaemia. It is a case of cardiac asthma when whistling rales and other clinical signs of obturation of the air passages arise in the heart patient during an attack of dyspnoea. In such a case the clinical picture resembles that of bronchial asthma. Sometimes the resemblance is so considerable that a physician with little experience may take an attack of cardiac asthma to be one of bronchial asthma.

Severe attack of paroxysmal dyspnoea may bring about pulmonary oedema the clinical picture of which develops as a result of a rapid passage of fluid from pulmonary capillaries to the alveoli. Today it is commonly held that the main causes of pulmonary oedema are a sharp rise in hydrostatic pressure in the pulmonary capillaries and an increase in the permeability of the pulmonary vessels.

Pulmonary oedema develops only when the pressure in the pulmonary capillaries exceeds the colloid-osmotic pressure of the plasma. It may be assumed that pulmonary oedema and an attack of paroxysmal dyspnoea in a myocardial infarction patient differ from each other only quantitatively. Exudation of oedematous fluid into the lumina of alveoli and bronchi and its accumulation in the interstitial tissue of the lungs are the necessary components of both clinical syndromes, but it is much more strongly pronounced in pulmonary oedema than in cardiac asthma.

Some clinicians consider the views on the intimate connection of cardiac asthma and pulmonary oedema with acute weakness of the left ventricle not convincing enough. Ariev (1962) found that in cardiac asthma the blood pressure remains normal and sometimes even rises, whereas the appearance of acute weakness of the left ventricle must, in his opinion, always be accompanied with a fall of arterial pressure. Confirming the correctness of the author's factual observations we should only like to call attention to the fact that the functional state of the heart and the minute volume are but one of the factors that determine the level of the patient's arterial pressure.

Wide employment of the method of catheterization of the cardiac cavities and pulmonary vessels made it possible to establish that the pulmonary capillary pressure may sometimes appreciably exceed the oncotic pressure of the blood plasma with no signs of cardiac asthma or pulmonary oedema appearing in the patients. This fact

was established during examination of mitral stenosis patients, and in our opinion, does not contradict the aforesaid view of the pathogenesis of cardiac asthma in myocardial infarction.

In appraising this fact it is necessary to take into account that the permeability of pulmonary capillaries in mitral stenosis patients is considerably diminished because of the thickening of the main membrane and the alveolar-capillary membrane of the lungs. Moreover, these patients always exhibit a compensatory increase in the function of the lymphatic vessels that drain the pulmonary tissue. The result of the action of these factors is that the exudation of fluid into the lumina of the alveoli of a patient with mitral stenosis begins at a higher pressure than in a healthy person.

Gelshtein (1951) also points out that the clinical picture of pulmonary oedema might be considered a result of cardiac failure 'but such an assumption is at variance with the fact that at this time tachycardia is not strongly pronounced (there are even cases of bradycardia) and a fall of arterial pressure is not always observed'. In his opinion, pulmonary oedema in myocardial infarction is a reflex reaction from the affected coronary vessels. The way of the reflex and the conditions under which it arises are not specified.

A similar point of view is that of Stupnitsky (1964) who holds that 'the initial cause of an attack of cardiac asthma in disturbances of coronary circulation is a burst of pathological impulsation in the myocardium' which reflexly evokes tachycardia. It is still not clear whether an attack of cardiac asthma can occur without tachycardia and cardiac failure.

The increase in the capillary pressure and the permeability of the pulmonary vessels is the main, but not the only cause of pulmonary oedema in myocardial infarction patients. A certain role in the pathogenesis of this complication is also played by other factors. While explaining cardiac asthma by acute left ventricular failure, Lang (1936) and Kurshakov (1947) assumed that its attacks also occurred in connection with changes in the state of the nervous system. In substantiating this point of view reference is usually made to the development of pulmonary oedema in cerebral strokes, encephalitis and cerebral traumas. Affections of the central nervous system lead to pulmonary oedema most likely through influencing the permeability of the pulmonary capillaries. The high therapeutic effectiveness of morphine in cardiac asthma is explained by many clinicians by the influence of this substance mainly on the central nervous system. According to Luisada and Cardi, a particularly frequent development of this complication in myocardial infarction is based on a reflex increase in the function of the sympathico-adrenal mechanism regulating homeostasis, combined with acute left ventricular failure.

Attacks of dyspnoea in acute left ventricular failure usually take place with increased pulmonary ventilation. The minute volume

of respiration, the respiration rate and the work of the respiratory muscles appreciably increase. It is usually held that these changes in respiration occur reflexly and that pulmonary tissue is a source of reflexes.

During acute left ventricular failure and the initial period of cardiac asthma the carbon dioxide pressure in the arterial blood usually falls. The oxygenation of the arterial blood remains normal.

With the development of pulmonary oedema the oxygenation of the arterial blood begins progressively to decrease owing to the disturbances in the processes of diffusion of this gas through the alveolar-capillary membrane of the lungs. The content of carbon dioxide in the blood noticeably increases for the same reason.

It is important to remember that in patients with chronic bronchitis, pneumosclerosis and other chronic pulmonary diseases involving disturbances in their respiratory function dyspnoea is observed before the development of infarction. Sometimes despite the severe dyspnoea the carbon dioxide pressure in the arterial blood of such patients may be appreciably raised. Acute left ventricular failure often develops in them on a background of elevated and not lowered carbon dioxide pressure in the arterial blood. These differences are of a certain practical importance, especially in choosing therapeutic measures when the picture is one of the acute left ventricular failure.

Pulmonary hyperaemia is manifested clinically in moist rales, the amount of which in a large measure depends on the severity of affection of the left ventricle. In mild cases only single moist rales are auscultated, and severe cases are attended with pulmonary oedema. Cardiac asthma or pulmonary oedema may be the first and even the only sign of myocardial infarction.

The attack always begins with a sensation of lack of air which soon develops into asthma. The respiration becomes loud and frequent. If the attack occurs at night the patient sits up in bed and rests on his arms. He is usually excited, his face expressing fear. The skin is pale and covered with droplets of sweat. During prolonged attacks cyanosis appears; at the height of an attack the patient coughs. In severe cases the coughing is accompanied with an excretion of a large amount of white or pinkish foamy sputum. Moist rales first appear in the postero-inferior parts of the right lung, then rapidly spread all over the lung, become resonant and are easily auscultated both in front and from behind. During an attack the respiration is sometimes whistling and bubbling.

The patient is usually frightened by the severity of his condition. He does not complain of pain in the chest, but, if the physician manages to calm him, it is nearly always possible, to reveal by special interrogation, not only the pain syndrome, but also to determine the irradiation of the pains. Our many years' clinical experience have convinced us that in myocardial infarction an attack

of cardiac asthma without concomitant pains in the chest is an exception rather than the rule.

In appraising the anamnesis it is necessary to remember that in cardiac asthma and pulmonary oedema complaints of pains in the chest are revealed the less frequently the more serious the patient's condition is. In very grave cases there are usually no complaints of pains in the chest. This circumstance is apparently the reason for the differences of some clinicians' opinion on the question of the incidence of pain sensations in the asthmatic form of myocardial infarction.

The analysis of the changes in haemodynamics arising in myocardial infarction warrants the assumption that the weakening of the contractile function of the left ventricle is the main, although not the only reason for pulmonary hyperaemia, which in mild cases leads to dyspnoea and in severe cases to orthopnoea, cardiac asthma and even pulmonary oedema. A clear clinical picture enables the physician confidently to diagnose the two latter syndromes.

We observed signs of pulmonary hyperaemia in cases of severe infarction on the radiographs of all the patients we examined on the first day of the disease. Dyspnoea and rales in the lungs were auscultated in 51 per cent of cases. Some authors also point out that X-ray signs of congestion in the pulmonary circulation are sometimes discovered in the absence of such physical signs as rales in the lower parts of the lungs. Bean (1937) observed dyspnoea in 38 per cent of patients. According to Chambers (1946), it is found in 86 per cent of cases. The differences of opinion on this essentially objective sign of the disease are probably due to the unequal severity of the cases and various age composition of the patients examined.

The incidence and extent of dyspnoea in the patients personally examined by us definitely depended on their age. Under the age of 60 dyspnoea was observed in 45.6 per cent of cases, over this age in 60 per cent. The higher incidence of dyspnoea in older patients is probably due to the affections of the heart and lung observed in them before the onset of the disease.

According to the data of archival case histories left ventricular failure was observed during the first week of infarction almost similarly often both in patients with a normal pressure (35.2 per cent) and in those in whom the pressure was raised before the illness (36.7 per cent). The development of acute left ventricular insufficiency is apparently determined not by the height of arterial pressure, but by other, more essential factors.

A survived myocardial infarction noticeably influences the development of acute left ventricular failure. According to Popov (1965), circulatory decompensation occurred in 60 per cent of patients soon after a recurrent myocardial infarction. We observed acute cardiac failure during a recurrent myocardial infarction in the first week of the disease in 42.8 per cent of cases, and in primary infarction in only 33.1 per cent. A former myocardial infarction

can, undoubtedly, be established with utmost precision on post-mortem examination. A special study of case histories and autopsy records of 230 fatal infarction cases enabled us to establish that in recurrent infarction acute left ventricular failure was observed in 56.1 per cent of cases and in primary infarction in 31.8 per cent. The difference in the incidence of acute left ventricular failure between the compared groups proved statistically significant ($p<0.01$).

The clinical picture of acute left ventricular failure is particularly often observed in myocardial infarction patients with a sclerotic or inborn stenosis of the aortic ostium. Attacks of cardiac asthma appear in these patients long before the infarction. In unfavourable cases, in addition to foci of fresh necrosis vast sclerotic fields are always found upon autopsy under the endocardium of a left ventricle which is usually sharply hypertrophied. The appearance of acute left ventricular failure in these cases is apparently due both to cicatricial changes in the myocardium and the affection of the papillary muscles, which is always observed.

Libman (1930); Fishberg *et al.* (1934); Pletnev (1936) and other authors tried to prove that occlusion of the left coronary artery leads to acute left ventricular failure, while thrombosis of the right coronary artery is manifested by the clinical picture of a rapidly growing failure of the right ventricle with a rise in venous pressure and formation of oedemas. Clinical and anatomical comparisons failed to establish any correlation between the localization of thrombosis and the type of occurring acute circulatory failure. Recently we endeavoured to verify once more the viability of this idea.

Vinogradov (1965) noted that infarction of the papillary muscles, unlike infarctions of the myocardium of other localization, usually begins with an attack of severe dyspnoea which often develops into asthma. Pains in the chest occur often, but dyspnoea develops in every case of infarction of the papillary muscles. An asthmatic state was observed both in isolated affections of the papillary muscles and in extensive cardiac infarctions with simultaneous affection of the papillary muscles.

The constancy and particularly pronounced character of left ventricular failure in these cases are apparently due in some measure to the affection of precisely the papillary muscles. In this localization of infarction the affection of the cardiac wall is accompanied with an acutely developing relative mitral failure with its characteristic rise in the blood pressure in the left atrium, pulmonary veins and pulmonary artery.

Extensive myocardial infarction without affection of the papillary muscles may also present a clinical picture of cardiac asthma. We should merely like to call attention to the fact that infarction of the papillary muscles and infarction in patients with a sclerotic defect or calcinosis of the aortic valve are always characterized by a picture of acute left ventricular failure which not infrequently end in pulmonary oedema.

The clinical picture of acute left ventricular failure most commonly arises in the beginning of the disease. Even in severe, but favourably terminating cases of infarction the attacks of cardiac asthma usually cease toward the end of the first week of the disease. This favourable variant of the course of the disease is encountered in about half the number of cases (Wright *et al.*, 1954). In unfavourable infarction cases the attacks of cardiac asthma usually reappear on the third week of the disease which assumes a protracted course.

Right ventricular failure in myocardial infarction is encountered much less frequently than left ventricular failure. We observed it in only 58 patients (10.9 per cent of cases). In 43 of them myocardial infarction was recurrent and in only 15 primary. Right ventricular failure is a natural result of infarction of the right ventricle. It also often develops in affection of the interventricular septum of the heart, which usually occurs together with an extensive infarction of the left ventricle.

This form of infarction was first described by Glagolev (1937). Its clinical picture and differential diagnosis were elucidated in greater detail by Speransky (1949) who suggested distinguishing oedematous and asthmatic forms of heart failure in myocardial infarction. Tetelbaum (1960) and Popov (1964) described it under the name of myocardial infarction with a rapidly developing total heart failure. They point out that this form of myocardial infarction most commonly develops in persons who had the hypertensive vascular disease during the pre-infarction period.

Failure of the right ventricle usually develops after all or nearly all signs of the acute period of the disease have disappeared. In typical cases three, less frequently four, weeks after the infarction signs of left ventricular failure recur or increase. Moist rales are auscultated in the lungs again. At night attacks of asthma appear. Soon the patient's liver begins to be palpated, and pitting of the shanks appears. The attacks of asthma somewhat decrease, but do not disappear completely. The clinical picture of total heart failure gradually develops; ascites appears; the venous pressure appreciably rises, but the rate of the blood flow decreases. This evolution of the signs of heart failure is most commonly observed after a recurrent or extensive primary infarction in patients with a left ventricular aneurysm and in patients with calcinosis or a sclerotic defect of the aortic valve.

Cardiogenic Shock

The experimental studies and clinical observations conducted by Lukomsky and Gratsiansky, Smetnev and other authors have convincingly demonstrated that every case of more or less severe myocardial infarction involves clinical or haemodynamic signs of heart failure. The method of continuous recording of the haemody-

namic indices has enabled us to show the development of the signs of heart failure during the very first minutes after ligating a coronary artery.

The unfailing appearance of these signs in every experiment gave some authors grounds to consider that acute circulatory failure in myocardial infarction is always heart failure and that shock in the myocardial infarction patient is a milder form of heart failure than pulmonary oedema.

In studying the haemodynamics in myocardial infarction in experiment and in the clinic Wiggers (1954) and other authors arrived at the conclusion that its changes in acute heart failure are indistinguishable from those that develop in shock. The main circulatory defect in both cases is manifested in a disparity between the capacity of the vascular bed and its contents. This disparity occurs in both cases as a result of the heart's inability to maintain the minute volume at a level adequate to the influx of blood to the affected ventricle. In experiment and in the clinic this is displayed by the rise of blood pressure before the affected ventricle. The affection of the left ventricle leads to the appearance of signs of pulmonary hyperaemia, while that of the right ventricle to elevated blood pressure in the right atrium and the veins communicating with it.

The similarity of the haemodynamic changes taking place in experiment during shock of various origin enabled some physiologists (Rushmer, 1961) to conclude that the term 'shock' may be completely replaced by a more concrete term, 'hypotension'.

Fascinated by the interesting ideas and seeing no patients the physiologist undoubtedly has the right to appraise any symptoms and signs of disease by the extent to which they are pronounced and the mechanism of their origination. It stands the clinician in good stead to use in his activity the findings of physiology. Because of the character of his activity he appraises not separate signs and mechanisms, but the whole picture of the disease.

Physiological studies have clearly shown that in the myocardial infarction patient hypotension is always of the same origin. Although acute heart failure may in some cases be as strongly pronounced as in shock, we believe it incorrect to use the term 'shock' in all cases of arterial hypotension. By accepting Rushmer's suggestion the clinician will have to unite in one group the conditions which sharply differ in their clinical picture, course, methods of treatment and prognosis.

Soviet clinicians have always distinguished acute heart failure from collapse or shock and regarded them as different forms of acute circulatory failure. Shock differs from acute heart failure not in the level of the arterial pressure, but in the patient's condition. Although the clinical picture of shock does not contain a single pathognomonic symptom, in typical cases the diagnosis of this complication is made without particular difficulties.

The special condition of a patient in cases of severe shock mani-

fests itself in extreme torpor. It is sometimes possible to discern that the torpor develops after a short period of excitement. The arterial pressure of such a patient is usually decreased, the pulse is soft, feeble and often quickened. The skin is pale, moist and cold. The visible mucous membranes have a cyanotic hue. This clinical syndrome may be observed in a patient for several hours and even days. The question of term with which this clinical picture should be designated cannot as yet be considered definitely settled. Some call it shock (Lukomsky, 1940), others collapse (Ganelina, 1970). Some authors simultaneously use both terms in describing the clinical picture of myocardial infarction.

In Soviet literature the term 'shock' usually designates a complex dystrophic process which begins with overexcitation of the central nervous system. The disturbances in haemodynamics and the humoral disturbances develop in this process secondarily. The aetiology of shock may vary. Most commonly it develops as a result of trauma, painful trauma in particular. These facts gave grounds to Moiseev to ascribe the appearance of the aforedescribed syndrome in myocardial infarction to the category of 'traumatic (in a broad sense) shock'.

Petrov (1962) divides shock into three stages in accordance with the changes in the functional state of the nervous system. During the first (erectile) stage the cerebral cortex is in a state of excitation, during the second (torpid) state it is inhibited. Upon exhaustion of the nerve centres shock develops into the third (irreversible) stage. In shock the disturbances in circulation are constantly observed, but the morbid process does not begin with them. They arise later.

By the term 'collapse' Petrov designates acute vascular insufficiency which is characterized by the development of inhibition in the vasomotor centres and other parts of the nervous system. The decrease of arterial pressure in collapse occurs as a result of decreased tonus of the vessels. The author holds that haemorrhagic collapse is a classic model of this state.

It should be noted, however, that vascular resistance to the blood flow in an acute and copious haemorrhage with hypotension at first sharply increases. According to Wiggers (1954) and other authors, the decrease in vascular tonus during an acute haemorrhage with severe hypotension occurs in about half the number of cases and only before the very death of the animal.

In the opinion of Soviet physiologists, the main difference between shock and collapse is that collapse begins with pathology of the circulation, whereas in shock circulatory pathology develops secondarily. Collapse and shock differ mainly in the early stages of the development. The deepening of these processes brings to the foreground features of similarity, and this has served as the basis for their identification.

Strazhesko (1955) regards collapse and shock as identical conditions. In his opinion, the characteristic feature and essence of any

shock is a circulatory disturbance and not a special state of the nervous system. While there is no sharp and sudden disturbance in circulation which is followed by a decrease in all vital functions of the organism, there is actually no shock. The condition we now call the erectile phase of shock Strazhesko designated by the term 'preshock condition'.

Most modern clinicians hold shock and collapse to be very similar, but not identical conditions. In Vinogradov's opinion, the onset of myocardial infarction is attended with a 'clinical picture of shock which in its development changes to collapse'. The latter is regarded as a continuation of shock, as one of its phases. Lukomsky also points out that the onset of myocardial infarction may be attended with 'shock and collapse', comprehending by the term 'collapse' the second (torpid) phase of shock.

In its time the hypothesis of the possible development of shock into collapse met with a strong objection on the part of Davydovsky (1958) who wrote that collapse is not the second phase of shock, that in collapse the functions of the cardiovascular system are not disturbed because of the impairment of the central inhibition apparatus.

If it is assumed that myocardial infarction is attended with shock, it must be admitted that the functions of the cardiovascular system are disturbed in this shock primarily and in no way because of the impairment of the apparatus of central inhibition.

According to literature, collapse and shock differ from each other rather in their central mechanisms because the changes in haemodynamics in them are identical. Both the personal experimental experience and the experience of other investigators bear convincing evidence that in occlusion of a coronary artery the changes in haemodynamics occur immediately after application of a clamp or tightening of ligature.

Wiggers (1954) specially recorded the time of the appearance of haemodynamic changes in myocardial infarction. The systolic ejection of the heart decreases during the very first second after occlusion of a coronary artery. Considering that the extramarginal inhibition in the central nervous system does not develop immediately after the infliction of a trauma, the disturbance in haemodynamics in myocardial infarction must, in accordance with the aforecited terminology of Soviet physiologists, be recognized as primary and be designated by the term 'collapse' rather than 'shock'.

The term 'traumatic shock' was first used only in the narrow sense of the word. This term designated the shock arrising after the infliction of a mechanical trauma. Pain was regarded as the main cause of shock, as its trigger factor. The term 'traumatic (in a broad sense) shock' was used to designate the shock that developed after application of pain stimulation and it was assumed that this pain stimulation did not have to be accompanied with mechanical trauma.

Of late many clinicians consider the foregoing point of view on the role of the pain factor in the pathogenesis of traumatic shock not sufficiently convincing. Meshalkin (1959), Amosov (1963) and other authors are inclined, on the basis of the advances of modern anaesthesiology, to dispute the leading role of the pain factor in the development of shock. The clinical experience of internists also indicates a possibility of the development of the typical clinical picture designated by the term 'shock' both in painful and painless forms of infarction. The pain sensations cannot apparently be regarded as the main or the sole reason for the development of shock in myocardial infarction.

Most clinicians hold that in the clinical picture of a shock condition in myocardial infarction it is always possible to find features that distinguish it from the clinical picture of traumatic shock. The skin of these patients is not only pale, cold and moist, but also has a cyanotic hue. Cyanosis is pronounced the more stronger, the graver the patient's condition is. If we add to this that the function of the circulatory apparatus is disturbed as a result of heart failure, the arbitrary character of using the term 'shock' in this disease will become manifest.

Very similar objections can be raised against using the term 'collapse', if the latter is conceived as a result of vascular paralysis. The total peripheral resistance in all the studied cases of myocardial infarction with a clinical picture of collapse turned out to be normal. Vascular failure develops only in the terminal stages of the complication. It must be added to this that classical haemorrhagic collapse begins and proceeds with a decreased flow of venous blood to the heart. The flow of blood to the heart in experimental myocardial infarction with prolonged and strongly pronounced hypotension proved to be normal. This fact does not make it possible to regard the haemodynamic disturbances in myocardial infarction as collapse.

The physicians of past generations diagnosed the patient's condition as shock and collapse not by the level of arterial pressure and not by the flow of blood to the heart, but by the general clinical impression they gathered from examining the patient. The level of the arterial pressure, the colour of the skin, the state of consciousness, the patient's reactivity and other symptoms and signs of the disease formed the total picture of these syndromes as their integral parts.

Formerly the term 'collapse' was used to designate the clinical syndrome which developed in infectious diseases usually during the crisis. The physicians were able to predict the onset of this syndrome which was manifested in the appearance of extreme weakness without loss of consciousness. At the same time the patient exhibited a low, soft pulse and sweated profusely. As was established later the arterial pressure decreased. The term 'shock' designated a special condition of the patient that sometimes occurred soon after

injury. Its clinical picture is vividly described in the works of Savenko (1834) and Pirogov (1941).

In the initial stage of myocardial infarction the patient sometimes develops a clinical picture which resembles that of shock and collapse. This complication is diagnosed by its specific clinical picture and not by the level of arterial pressure or any other single strongly pronounced sign. Numerous studies have shown that in the myocardial infarction patient this clinical syndrome is combined with such haemodynamic disturbances that are not found either in traumatic shock or in haemorrhagic collapse (Vinogradov).

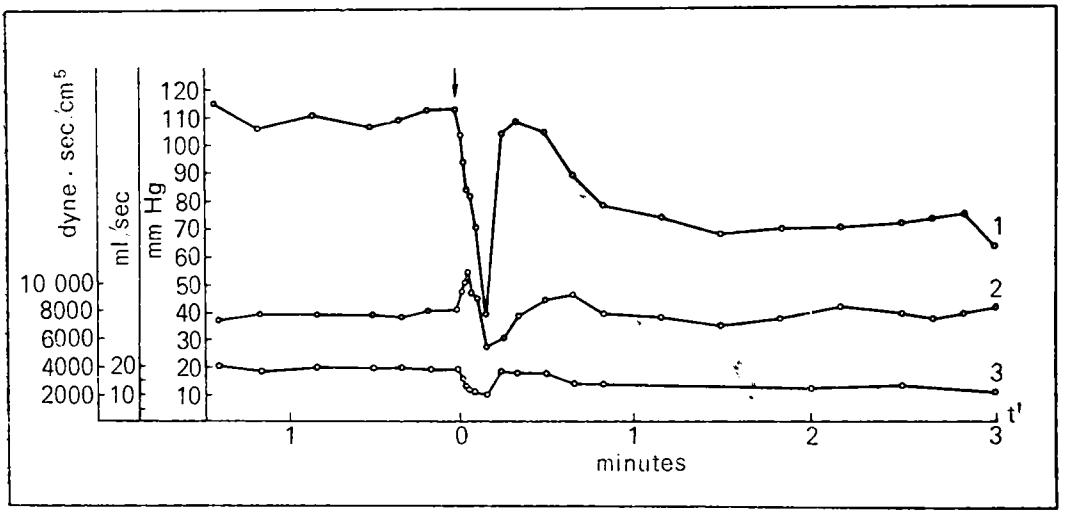

Fig. 55. Change in arterial pressure (*1*), general peripheral resistance (*2*) and minute volume of the blood (*3*) in experimental myocardial infarction with a fall of arterial pressure to the level of shock

The patient's special condition which is usually designated in the clinic by the term 'shock' may arise in various types of haemodynamic disturbances. It may be observed in patients with high, normal and low arterial pressure. The variations in arterial pressure during myocardial infarction are determined by the correlation between the minute volume and the vasomotor tonus. We should only like to call attention to the differences in reactions of the vasomotor tonus in acute heart failure and shock.

According to the generally accepted criteria, it may be a case of experimental shock when under the influence of the experimenter an animal exhibits a sharp fall of arterial pressure of not less than one-third of the initial level.

The changes in vasomotor tonus in such an experiment are shown in Fig. 55. A sharp decrease in the minute volume was accompanied with oppositely directed deviations of the general peripheral resistance which alternately fell below and rose above the initial level. The wavelike variations around the initial level gradually became

less strongly pronounced, and after a certain period, before the animal's death, the general peripheral resistance became fixed below the initial level either because of the unresponsiveness of the executive organs or the exhaustion of the nerve centres which regulate the vasomotor tonus. This is the terminal phase, the period of depression of all the adaptive reactions.

Phasic variations in arterial pressure are noted simultaneously with the phasic changes in vasomotor tonus. Immediately after occlusion of a coronary artery the arterial pressure sharply falls. After this it temporarily rises and then begins its second progressive decrease which indicates the development of deep and irreversible disturbances in the central regulation of this haemodynamic index. The phasic variations in minute volume in shock are less vividly pronounced, but their existence nevertheless seems sufficiently convincing.

An analysis of the changes in the general peripheral resistance warrants the assumption that the development of shock is accompanied not only with vasoconstriction, but also with vasodilatation in the systemic circulation. During the shock vasodilatation gradually increases in intensity and during its terminal period clearly dominates over vasoconstriction.

As was already noted, in cases of uncomplicated infarction vasodilatation is also sometimes observed, but only during the incipient period of the disease. Subsequently the general peripheral resistance noticeably and constantly increases indicating a marked predominance of processes of vasoconstriction. The wavelike (phasic) changes in vasomotor tonus in shock and its more or less constant increase in acute heart failure are probably best explained by an unequal functional state of the nerve centres, a predominance of processes of excitation in them in cases of heart failure, and a development of transmarginal inhibition in them after the period of phasic changes.

The functional changes occurring during the incipient period of uncomplicated infarction are always reversible. At this time the characteristic picture of shock does not develop because the aforementioned changes still belong to the adaptive reactions of the transitional period during which derangements of only separate adaptive reactions occur, while other adaptive mechanisms may even function intensively. We see a vivid example of the correctness of this proposition in the increase in the general peripheral resistance which is regularly observed in most cases of relatively mild infarction.

The onset of the torpid phase of shock (collapse) is characterized by the depression of most of the adaptive mechanisms. The reason for it is probably a disturbance in the regulatory influences of the central nervous system developing as a result of its exhaustion and the spread of diffuse transmarginal inhibition over it.

Haemodynamic manifestation of this are progressive fall of the

arterial pressure, decrease in the minute volume and progressive lowering of the general peripheral resistance.

The peculiarity of shock in myocardial infarction is that the phasic changes in vasomotor tonus during this condition appear on a background of contractile insufficiency of the heart.

Phasic changes in the general peripheral resistance are also observed in acute heart failure when the arterial pressure is still maintained at a normal level. It follows that the incipient phases of shock arise long before the development of critical hypotension. The arterial pressure begins to decrease catastrophically probably because of the development of transmarginal inhibition in the region of the vasomotor centre, owing to which the patient's organism proves to be unable to increase the vasomotor tonus to the extent where it equals the decrease in the minute volume.

In summing up the foregoing data we may say that in myocardial infarction shock is a more or less protracted process in which three periods can be distinguished. The first period is accompanied with mobilization of the adaptive mechanisms whose activity is aimed at eliminating the main haemodynamic defect produced by the contractile failure of a more or less large part of the myocardium. The activity of these adaptive mechanisms leads to an increase in the general peripheral resistance.

The afferent impulsation from the affected organ combined with the results of the sharp decrease in the minute volume leads to the development of phasic phenomena in the vasomotor centre. In cases of an unfavourable course this period of relative stabilization of the process is succeeded by the second period during which most of the adaptive mechanisms are disrupted and the arterial pressure, general peripheral resistance and the minute volume are decreased as a result. Prolonged hypotension gives rise to a vicious circle which fosters a transition of shock to the next, irreversible period with characteristic metabolic disturbances and failure to react to therapy.

Consequently, the development of transmarginal inhibition in the vasomotor centre, by preventing the exhaustion of its energy resources, becomes the cause first of the limitation and then of a disruption of the organism's compensatory and adaptive reactions. This proposition is not at variance with the opinion of many authors on the protective role of transmarginal inhibition. In the vasomotor and other nerve centres and ganglia it always plays a protective role only for the nervous system itself because it prevents the nerve cells from total functional exhaustion.

The second aspect of transmarginal inhibition is manifested in that its development appreciably disturbs the functions of the regulated mechanisms. Transmarginal inhibition of the vasomotor centre, in particular, leads to a relatively insufficient increase in the vasomotor tone and becomes one of the causes of severe hypotension.

Generalization of the clinical and experimental findings warrants the assertion that in myocardial infarction patients left ventricular failure is sometimes accompanied with another process which the Soviet clinic and physiology commonly designates by the term 'shock'. The early stages of this process may sometimes be observed in patients with a clinical picture of acute heart failure; its later stages are manifested as a clinical picture of shock.

Although the so-called peripheral signs of collapse are often observed in patients during acute heart failure, clinical tradition, nevertheless, distinguishes shock and acute heart failure as separate forms of acute circulatory failure. This tradition rests on clinical experience which requires from the physician an ability correctly to diagnose these conditions and differentiate their therapy.

The incidence of shock in myocardial infarction has not been established precisely. According to Vinogradov (1965), this complication occurs in about 4.5 per cent of patients. Gurevich (1960) observed it in 57.5 per cent of cases, Lukomsky (1964) in 22.8 per cent and Sivkov *et al.* (1965) in 25.6 per cent. The difference in the figures cited by the various authors can be explained by the two main factors, namely, the differences in the diagnostic criteria of shock and the peculiarities of the clinical course of infarction. The role of the former is now recognized by all clinicians; the role of the latter is known less.

Until recently clinicians had no common diagnostic criteria of shock, and every one, therefore, diagnosed this complication on the basis of his own criteria. Anglo-American and Scandinavian authors say that the height of arterial pressure is the most unreliable criterion of shock, yet diagnose this complication on the basis of a rapidly occurring and strongly pronounced fall of precisely this haemodynamic index. Zolotova-Kostomarova (1961) and other clinicians diagnose shock each time the patient exhibits so-called shock phenomena. Smetnev (1966) considers it possible to diagnose shock in cases of subnormal and even normal arterial pressure.

Many works cite only generalized characteristics of the clinical picture of shock without indicating the quantitative aspect of the particular sign. In describing this complication Nezlin (1956) mentions as necessary symptoms only hypotension and slow pulse without indicating quantitatively either the height of arterial pressure or the pulse rate. In some works, even specially devoted to the clinical aspects of shock (Tetelbaum, 1960), the diagnostic criteria of this syndrome are not mentioned at all.

The extreme variety of diagnostic criteria of shock makes it very difficult to compare the findings of the different researchers and evaluate the effectiveness of the therapeutic measures suggested by them. More or less uniform criteria have been suggested of late; they include the height of arterial pressure, on the one hand, and such symptoms and signs as weakness, torpor, and characteristic changes in the skin, pulse and micturition, on the other. Many cli-

nicians refer to these signs as peripheral because they arise as a result of dysfunction of peripheral (with respect to the heart) organs.

In accordance with the new criteria it is suggested that shock should be diagnosed only in infarction cases where the systolic arterial pressure falls at least to 80 mm Hg. In cases of mild shock hypotension lasts for twenty to forty minutes. In cases of severer shock sharp hypotension persists for about an hour and longer. After this the arterial pressure may temporarily rise, sometimes even to the normal level.

The fall of arterial pressure below 80 mm Hg is attended with a clinical picture of shock in many, but not all cases of myocardial infarction. This circumstance necessitates a search for other and more reliable diagnostic criteria of shock. It has been suggested that the complication should be diagnosed by the level not of the systolic, but the pulse arterial pressure. When this criterion is employed, there is no need to know the level of the arterial pressure prior to the disease.

Many clinicians endeavoured to ascertain the diagnostic value of this criterion. Smetnev (1966) points out that the patient's condition is determined more precisely by the pulse than systolic arterial pressure. Although he regards a pulse pressure below 25 mm Hg as a characteristic sign of cardiogenic shock, in many of his cases with a marked picture of this complication the pulse pressure was 45 mm Hg, i.e. normal.

On the basis of our own experience we can say that there are usually no signs of shock with a pulse pressure above 30 mm Hg. Pulse pressure below 20 mm Hg is usually not observed without the peripheral symptoms of this complication. The disappearance of shock was noted only in cases where the pulse pressure was above 25-30 mm Hg. The presence of peripheral symptoms of shock at an arterial pressure of 100/80 mm Hg and their absence at 80/40 mm Hg cannot be regarded as anything unusual.

We consider the attempts to use the pulse pressure as a diagnostic criterion of shock unrealistic mainly because it is extremely difficult to determine the diastolic pressure by Korotkov's method in this complication. Practically, as Helander (1949-50) justly points out, it is possible to obtain erroneous rather than actual figures.

Peripheral symptoms of shock (some authors call them 'shock phenomena') sometimes appear in myocardial infarction patients with a normal or even increased arterial pressure. The latter is particularly often observed in persons formerly affected with hypertensive vascular disease. On this basis some Scandinavian authors diagnose cardiogenic shock at a systolic arterial pressure of 130-140 mm Hg.

Smetnev (1966) also holds that in a patient with hypertension cardiogenic shock can be diagnosed when the arterial pressure has

fallen to subnormal and normal figures. A clinical picture of shock was described even in myocardial infarction patients with a systolic arterial pressure above 200 mm Hg.

The foregoing clinical observations warrant the assertion that a characteristic clinical picture of shock with the appearance of torpor, profuse sweating and pronounced signs of centralization of blood circulation may develop in a patient not only at a low, but also at a normal and even high level of the arterial pressure. These observations efface, as it were, the differences between shock in myocardial infarction and traumatic shock whose clinical picture arises, as is known, at any level of arterial pressure. These observations in some measure also efface the clear boundary between shock and acute heart failure.

It should be remembered, however, that in cardiogenic shock the patient's torpor is much less pronounced than in traumatic shock. The absence of torpor is one of the signs that enables one to differentiate acute heart failure from shock. The clinical signs arising in connection with the centralization of blood circulation are equally vivid in all these states.

The level of the arterial pressure and the markedness of the so-called shock phenomena taken alone, without any connection with the whole clinical picture of the disease, proved to be not insufficiently reliable diagnostic criterion of certain forms of acute circulatory failure. At the present time most clinicians, therefore, diagnose shock in myocardial infarction patients by the totality of the clinical signs.

Regarding shock as a result of disruption of the regulatory mechanisms we diagnose this complication only in cases where the fall of systolic arterial pressure (usually to 80 mm Hg) is combined with the appearance of clinical signs of circulatory centralization. In such patients it is usually also possible to reveal a more or less marked general weakness and torpor. By using these criteria we diagnosed shock in 26 per cent of myocardial infarction cases.

Although most of the modern authors diagnose shock on the basis of fairly strict criteria, the reports of its incidence in myocardial infarction still noticeably differ from each other. This may be explained by the differences in the age of the examined patients, their initial condition and certain other factors. But in addition to the generally known reasons there is one more, and, in our opinion, very important reason which manifests itself not directly, but through interaction with the system of hospitalizing patients prevailing in various cities of the Soviet Union. This reason is one of the peculiarities of the clinical course of infarction.

It was formerly held that shock can arise only 'in the very first hours of the disease' (Gulo, 1965). By analogy with traumatic shock Selzer (1952), Kyandzuntseva (1956), Ganelina (1970) and others distinguish in myocardial infarction early, reflex shock that arises simultaneously with the pains, and a severer cardiogenic shock oc-

curring in vast myocardial infarctions usually 5-36 hours after the onset of the disease.

Nezlin (1956) supposes that shock may occur not only in the first hours, but also in the first days of the disease. While studying this problem repeatedly in connection with administration of vasopressors, Vinogradov (1962), Popov (1965), Smetnev (1966), Yanushkevichus (1970) draw attention to the fact that shock may occur at later periods of the disease.

Exact knowledge of the periods when shock may arise is very important in organizing the most effective medical aid for the patients. To elucidate the problem, we determined the periods of the development of this complication in 140 cases and discovered the difference in the periods of the appearance of shock in infarctions beginning suddenly and in those with a more or less prolonged prodromal period. When the onset of myocardial infarction was acute, shock was, as a rule, noted on the very first day of the disease. When the infarction began with a series of angina pectoris attacks, shock appeared in most cases between the second and fourth day.

Today it is customary to hospitalize all myocardial infarction patients in the very first hours of the disease with the result that cases of shock arising both in the very beginning of the infarction and several days after the onset of the disease are recorded. Only a few years ago infarction patients were usually hospitalized one or two weeks after the beginning of the disease. So it was natural that the reports of clinicians of that time (Vinogradov *et al.*, 1963) did not cover all cases of shock, but only those that arose some time after the onset of the infarction. The true incidence of this complication is undoubtedly more precisely recorded in the most recent reports.

Shock most commonly arises on a background of an intense pain attack. Some authors point at the existence of a direct link between the duration of the pains and the severity of the shock. It is probable that a more important part is played by the intensity and not the duration of the pains. Many clinicians are inclined to consider pain the principal cause of the shock itself and the developing haemodynamic disturbances.

Pain is undoubtedly not immaterial for the organism, but we should like to call attention to the fact that it is not an indispensable symptom of this complication. Moreover, clinical experience shows that the graver the patient's condition the more often he has no sensation of pain. Even by persistent questioning Smetnev (1966) failed to find any pain sensations in 2.5 per cent of infarction patients with a clinical picture of cardiogenic shock. Tetelbaum (1960) suggests distinguishing a special, collaptoid form of myocardial infarction with a total absence of the pain syndrome as its characteristic sign.

The role of the pain factor in the pathogenesis of shock should be neither overestimated nor underestimated. Personal experience

warrants the assertion that with intensification of pain the clinical manifestations of shock become more strongly pronounced. Termination of the pain attack is usually accompanied with a gradual disappearance of its signs.

An increase in the heart rate was formerly considered an indispensable sign of shock. Later it was shown (Kurshakov, 1947, and Lukomsky and Tareev, 1958) that tachycardia is the most frequent, but not the only reaction of the heart to the development of shock. In shock the heart rate may either increase or decrease, bradycardia usually lasts a short time, while tachycardia is a more stable sign of this complication, its persistence being observed in severe shock which arises and runs its course on a background of progressively increasing heart failure.

The severity of shock can be determined in most cases not so much by the markedness as by the duration of arterial hypotension.

Clinical manifestations of shock may be observed, as was already pointed out, at any level of the arterial pressure, but when the arterial pressure cannot be determined for a long time the therapeutic measures usually prove ineffective. Antonnen and Rautakoski (1956) were unable to save the life of a single patient in whom they could not determine the arterial pressure by auscultation.

Circulatory centralization ensures primarily the blood supply to vitally important organs, but when the systolic arterial pressure falls below 60 mm Hg the blood supply of the brain and heart becomes absolutely insufficient. In our experience the patient's capacity to restore the normal pressure lasted only in cases where it fell below the aforesaid critical level only for a short time.

The markedness of the clinical signs arising in connection with circulatory centralization definitely depends on both the absolute level of the arterial pressure and the rate and extent of its fall. A rapid fall of arterial pressure from 220 to 150 mm Hg is often accompanied with the appearance of peripheral signs of shock. The attempts of some authors to diagnose shock in these patients and determine its severity must be recognized as unconvincing.

All cases of tachycardiac arrhythmias aggravated by a clinical picture of shock should apparently be regarded as severe. Considering the peculiarities of its course and therapy Chazov (1970) and Ganelina (1970) single it out as a special form of arrhythmic shock. In 1957 Vinogradov pointed out that the severity of shock in acute myocardial infarction can be with the utmost accuracy determined by the type of the response reaction of the cardiovascular system to the administration of vasopressors. Depending on the type of the pressor reaction it is possible to distinguish mild and severe shock.

In cases of mild shock the pressor reaction is usually accompanied with a disappearance of its signs and a restoration of the patient's capacity independently to maintain the arterial pressure

at a normal level. The systolic and diastolic pressure rises, the former always to a greater extent than the latter. The pulse pressure increases. Tachycardia disappears. Repeated falls of arterial pressure in this type of shock are rare.

In cases of severe shock the pressor reaction is often pronounced not sufficiently. In many cases it is possible to intensify it by additionally administering strophanthin or by increasing the dose of the vasopressor. The systolic arterial pressure rises to a lesser extent than the diastolic pressure. The pulse pressure remains low. Tachycardia usually does not disappear. Despite the normal systolic arterial pressure profuse sweating occurs periodically. By administering larger doses of vasopressors and strophanthin it is possible to eliminate hypotension, but in severe shock the natural pressor influences are not immediately restored, owing to which the fall of arterial pressure often recurs and shock assumes a protracted course.

The severity of shock definitely depends on its duration. This criterion of severity is unanimously recognized by all clinicians. This is apparently due to the fact that the prolongation of shock progressively disturbs the blood supply to all organs and tissues, which inevitably leads to an increase in heart failure, the development of metabolic acidosis and apparently a complete or almost complete disconnection of separate vascular regions from the central circulation. Cases of especially severe shock are accompanied with pulmonary oedema and azotaemia.

Yasakova (1957) and Meerzon (1958) point out that in myocardial infarction shock most commonly develops in younger patients. In Smetnev's observations (1966) myocardial infarction was aggravated by cardiogenic shock in 53 per cent of patients over the age of 60 and in 38 per cent between the ages of 50 and 60. The opposite results of these fairly extensive reports show that the development of shock is determined not by the patient's age, but by some other factors. Raevskaya (1955) noticed that irrespective of the effect of other factors, phenomena of marked shock in myocardial infarction occur rather often in persons whose arterial pressure before the disease was normal or below normal. We also found that in hypertensive patients myocardial infarction is aggravated by shock somewhat less frequently than in patients with normal arterial pressure.

The results of these observations confirm the correctness of the concept of the critical level of the arterial pressure. In hypertensive patients the fall of arterial pressure in absolute figures is often even more pronounced than in patients with normal pressure, but in the latter the arterial pressure more often falls below the critical level, which excludes the possibility of effective perfusion of the brain and heart.

According to Popov (1965), in recurrent infarction shock arises many times as often as in primary infarction. Vinogradov (1965) could not confirm this. Many authors point out that women

have shock less frequently than men, but it runs a much severer course. This opinion could be considered substantiated if its adherents rested on indices of the incidence and severity of shock in men and women standardized according to age. Unfortunately not a single adherent of this assertion took into account that women have myocardial infarction at a more advanced age than men and that age noticeably alters the prognosis not only of the infarction, but also of its complications.

Shock most commonly occurs in cases of extensive myocardial infarction. The extent of the affection is an essential, but not the only factor that predisposes to this complication. Shock may also develop in microfocal, especially recurrent, infarction (Popov, 1965).

Thus myocardial infarction is sometimes aggravated by shock. By clinical tradition this complication is regarded as a special, independent form of acute circulatory failure. Shock has a characteristic clinical picture and can be confidently diagnosed on the basis of a peculiar complex of clinical symptoms and signs.

The suggestion of some physiologists to relinquish the term 'shock' is not convincing enough because the disturbances in haemodynamics are but one of the causes of the formation of its clinical picture.

The diagnosis of shock imposes upon the physician the duty of prescribing for the patient a certain complex of therapeutic measures which are carried out only in cases of this complication of infarction. The peculiarity of the haemodynamic disturbances, the clinical manifestations and the specificity of therapeutic measures are the main arguments in favour of recognizing shock as an independent form of acute circulatory failure in myocardial infarction.

Disturbances in the Cardiac Rhythm

Myocardial infarction can cause all the known disturbances in the rhythmic activity of the heart. Some of these arrhythmias are of a short duration, lasting three to four seconds, while others, arising in the acute period of the disease, may persist for the rest of the patient's life. Combining with myocardial infarction some arrhythmias do not noticeably affect the course of the disease, while others often serve as the cause of fatal results.

The improvement of the methods of controlling left ventricular failure and shock was accompanied with an appreciable decrease in mortality from these complications with the result that mortality from disturbances in the cardiac rhythm has of late relatively increased. When arrhythmia is the dominant syndrome in the picture of infarction, its other clinical signs are often less clearly manifest. Acute heart failure develops in cases of tachycardiac arrhythmia mainly because of the shortening of the diastole and the specific redistribution of the minute volume with an accumulation of blood in the system of low pressure vessels (Wiggers, 1954).

Both ventricular and supraventricular tachycardia is often the

cause of pain sensations in the chest. During an attack of tachycardia the signs characteristic of myocardial infarction frequently disappear from the ECG and appear only after establishment of the sinus rhythm (Gurevich and Kelman, 1968).

It is accepted that the appearance of arrhythmia in myocardial infarction appreciably deteriorates the prognosis. Mortality from infarction with marked rhythm disturbances is about twice as high as it is with normal rhythm (Vinogradov, 1965). The condition of patients with tachycardiac arrhythmias is usually grave and the physician must, therefore, make a correct diagnosis and prescribe the treatment without waiting for the tachycardia to cease spontaneously.

The reports of different authors on the frequency of rhythm disturbances noticeably differ from each other. On an extensive material Mikhnev *et al.* (1966) observed disturbances in rhythm and conduction in 33.7 per cent of patients, Popov (1964) found rhythm disorders in only 26.7 per cent, whereas Kheinonen (1965) in 69.4 per cent of cases of recurrent myocardial infarction. Sumarokov (1965) found arrhythmia at least in 31 per cent of the infarction cases, while Mironova (1963) in 42.6 per cent. According to Lukomsky and Tareev (1957), the disturbances in rhythm and conduction were observed in 54.3 per cent of patients. Teodori (1953) observed the disturbances in rhythm in 47.8 per cent of cases, Makolkin (1957) in 39.7 per cent, and Zhdanova (1958) in 35.7 per cent; Litova (1967) found them in 30 per cent of myocardial infarction patients.

The reports of many of the foregoing authors are based on results of examinations of a very large number of patients, and the divergences between the various statistics are probably due to the difference in the frequency and time of their ECG examinations. It is known that most of the rhythm disturbances in myocardial infarction are of a short duration and that they most commonly occur in the first days of the disease. The farther from the beginning of the disease the less frequent the disturbances in the cardiac rhythm. Some authors, e.g. Mikhnev, considered it more appropriate to exclude from their reports the patients who had rhythm and conduction disturbances before the disease, as well as patients with sinus tachycardia and bradycardia. Others, on the contrary, took into account the arrhythmia of all myocardial infarction patients.

Of late the method of continuously watching the activity of the heart with ECG records has become increasingly more used. This method has enabled one to obtain incontestable data on the time of the appearance, the duration, frequency and forms of disturbance in the cardiac rhythm during myocardial infarction.

The results of long-term electrocardiographic observation show that in myocardial infarction arrhythmia occurs much more frequently than any of the aforementioned authors reported. According to Schröder *et al.* (1966); Chazov and Ruda (1967), and Goldberg (1969), rhythm disturbances take place in 80-95 per cent of

myocardial infarction cases, extrasystole being the most common disturbance. The second most frequent disturbance is cardiac fibrillation, and the third one is that in conduction. Nodal rhythm, interference with dissociation, ventricular tachycardia and atrial flutter occur much less frequently.

Ventricular fibrillation proved to be the most frequent cause of sudden death of myocardial infarction patients. It was formerly considered to be an irreversible complication that always ended in the patient's death. The method of continuous electrocardiographic observation enabled one to record ventricular fibrillation in about 10 per cent of patients and to demonstrate very convincingly its reversibility.

It turned out that many of the noted disturbances in cardiac rhythm often occurred without any subjective sensations. Spann *et al.* (1964) reported that eight patients out of eleven completely failed to notice the attacks of ventricular tachycardia. They were very brief and ended spontaneously like the attacks of some other disturbances in cardiac rhythm.

The results of employing the new method of studying the rhythmic heart activity are extremely important in understanding many problems of the clinic and treatment of myocardial infarction. But before reconsidering these problems it was necessary to make sure whether similarly symptomless disturbances in cardiac rhythm occur also in healthy people. Such a study was conducted by Spann *et al.* (1964). They examined nine patients the first time eight hours and the second time seven months after the onset of the disease. Each time the cardiac rhythm was traced over a period of 52 hours.

During the acute period of the disease there were 20 attacks of arrhythmia, each of them ending spontaneously. After recovery a spontaneous appearance of brief arrhythmia was noted in only one patient. The difference in the frequency of the disturbances in cardiac rhythm during the compared periods was too big to be considered accidental.

The rhythm disturbances in myocardial infarction are most commonly displayed as extrasystoles. By using the method of long-term recording of the cardiac rhythm Hurwitz and Eliot (1964) showed on a considerable number of patients that ventricular extrasystoles appear in 80 per cent of myocardial infarction cases. Teodori (1956) noticed that left ventricular extrasystoles most commonly occur in infarction of the anterior wall, and right ventricular in infarction of the posterior wall. Supraventricular extrasystoles were formerly thought to be a rare complication of infarction. The new method has revealed them in 70 per cent of myocardial infarction patients.

Lukomsky (1964) points out that rare extrasystoles arising from the same site do not indicate a poor prognosis, while polytopical frequent ventricular extrasystoles may herald the onset of ventricular tachycardia. Atrial and nodal extrasystoles cannot become

the direct causes of attacks of ventricular tachycardia and therefore are not of any adverse prognostic significance.

It was formerly considered that ventricular tachycardia was a rare complication of myocardial infarction. According to Julian *et al.* (1964); Bashour and Edmondson (1965); Kurland and Pressman (1965); Goldberg (1969); Lukomsky and Doshchitsyn (1969), and other authors, who used the method of long-term observation, ventricular tachycardia arises in about 12 per cent of myocardial infarction patients, while its attacks, as was shown by Moiseev and Ustinova (1967), are often brief and symptomless, and end spontaneously. Prolonged attacks of ventricular tachycardia occur much less frequently. The appearance of an ectopic focus of excitation in the cardiac ventricles is accompanied with their tachysystoles. The atria contract independently of the ventricles, being subordinated to the automatism of the sino-atrial node.

Short attacks of ventricular tachycardia can be diagnosed only on an electrocardiogram. Subjectively they are perceived as interruptions in the cardiac rhythm or a pain sensation. Sometimes they are unnoticed. A reliable diagnosis of longer attacks can also be made only after an ECG analysis. Physical signs warrant only a suspicion of ventricular tachycardia. In myocardial infarction the attacks of ventricular tachycardia usually follow each other, a sinus rhythm or any other disturbance in cardiac rhythm being observed in the intervals between them.

In most cases the attack begins at once. It is very rarely preceded by separate extrasystoles. Patients perceive attacks of ventricular tachycardia as palpitation which may last several hours or days. The sense of constriction of the chest sometimes develops into a sense of pain behind the sternum. We happened to observe the cessation of an attack being followed by the disappearance of painful sensations behind the sternum. The appearance of pain was apparently connected with the decrease in the coronary blood flow during an attack. Protracted attacks of ventricular tachycardia lead, as a rule, to the development of severe heart failure and shock.

The rate of ventricular contractions usually does not exceed 150-180 per min. In auscultation the attention is attracted by the changing intensity and timbre of the first sound over the heart apex. This sign reliably distinguishes ventricular tachycardia from supraventricular (paroxysmal) one in which the strength of the first sound remains the same all through the attack.

Prolonged auscultation makes it possible to reveal the second important diagnostic sign of ventricular tachycardia, i.e. the rate of ventricular contractions may differ by five-seven beats in separate minutes of auscultation. The ventricular activity in paroxysmal supraventricular tachycardia is known to be always strictly rhythmic.

Irrespective of the duration of an attack the prognosis in ventricular tachycardia is always serious because not only its long, but

also short paroxysms may develop into ventricular fibrillation and become the cause of sudden death.

During the acute period of myocardial infarction sudden death occurs so often that it is even used for retrospective diagnosis of this disease. Sudden death sometimes also occurs during the period of convalescence, its main causes being embolism of large branches of the pulmonary artery, external or internal ruptures of the heart, ventricular fibrillation and cardiac arrest. The last two complications are usually considered the direct causes of sudden death in all cases where autopsy fails to find any other factors that may unexpectedly terminate life.

In the numerous cases observed by Lukomsky and Doshchitsyn (1969) sudden death connected with disturbances in cardiac rhythm was noted in 5.65 per cent of myocardial infarction patients and in 26.7 per cent of those who died of this disease. In about half the cases it occurred during the first two days after the onset of infarction. Ventricular fibrillation was responsible for 75 per cent of sudden death while in the remaining 25 per cent the circulation was arrested owing to other disturbances in the cardiac rhythm or asystole.

According to various authors, cardiac fibrillation occurs in about 13-15 per cent of myocardial infarction patients. As in ventricular tachycardia it usually occurs in the form of short paroxysms which often terminate spontaneously. In some cases the attacks of cardiac fibrillation are symptomless, while in others they are accompanied with pains in the chest, which are often regarded as attacks of angina pectoris. Their true source is sometimes ascertained only after electrocardiography. James (1961) and Pevzner (1962) point out that in a thorough histological examination signs of microfocal affections of the atria can be found in most of these patients.

In the beginning of myocardial infarction, the tachycardiac form of cardiac fibrillation is usually observed. The prognosis is the more serious the higher the heart rate. Signs of acute heart failure or shock usually develop at a frequency of ventricular contractions of about 150 per min. In such cases conditions often arise requiring urgent therapeutic measures.

Paroxysms of cardiac fibrillation usually terminate spontaneously several minutes or hours after their onset. Cardiac fibrillation tends to become constant only in patients with marked cardiosclerosis and a sharp enlargement of the heart.

Short attacks of cardiac fibrillation do not noticeably deteriorate the prognosis, but when the paroxysm is prolonged or is aggravated by a clinical picture of shock the prognosis becomes serious. According to Lukomsky and Tareev (1958), mortality is three times as high among myocardial infarction patients with cardiac fibrillation as among those with a sinus rhythm.

Atrial flutter seldom occurs in myocardial infarction. This complication is usually of a transient character.

Sometimes it is necessary to differentiate a paroxysm of cardiac fibrillation from attacks of paroxysmal and ventricular tachycardia. The changing resonance of the first sound and the instability of cardiac rhythm distinguish paroxysms of cardiac fibrillation from paroxysmal tachycardia. Guided by the foregoing signs it is usually possible to differentiate these forms of arrhythmia without resorting to electrocardiography. Cardiac fibrillation is characterized by a milder course of an attack and a slower development of heart failure than is ventricular tachycardia. In ventricular tachycardia the jugular veins begin to swell during the very first ten to fifteen minutes of an attack, whereas in cardiac fibrillation this sign is usually observed much later.

The rhythm initiated by the atrioventricular node occurs in 18 per cent of myocardial infarction cases, while tachycardia initiated by the atria or the atrioventricular node takes place in 2-6 per cent of cases. The prognostic significance of the latter is nearly always serious.

If myocardial infarction begins with an attack of paroxysmal tachycardia, there are usually no signs of it on the ECG. They appear only after cessation of the attack. The atypical character of the ECG changes is often combined with an atypical pain syndrome thereby making the timely diagnosis of infarction very difficult.

Unlike cardiac fibrillation, attacks of paroxysmal tachycardia are characterized by stability. Without treatment they last several days (Mironova, 1963) or even weeks (Friedberg, 1966). Paroxysmal tachycardia most commonly arises not in the very beginning of the infarction, but one or three days after it. With its appearance the condition of the patients sharply deteriorates. Acute heart failure and sometimes shock usually develop. Chazov distinguishes this form as a special 'arrhythmic' shock.

Conduction disturbances in myocardial infarction were studied by Kozhevnikov, Lukomsky, Matusova, Zhdanova, and others. It was found that they occur fairly often. They appear, as a rule, in the first week and particularly often on the first or second day of the disease. A slowing of atrioventricular conduction is found in about 30 per cent of cases. It is equally frequently found in anterior and posterior infarctions, is usually transient in character and runs without clinical signs.

The marked fluctuations of the *P-Q* interval in the course of the disease are associated by Lukomsky and Friedberg with disturbances in coronary circulation and with the appearance and disappearance of fresh necrobiotic foci in the myocardium. Chernogorov (1962) explains the disturbances of atrioventricular conduction in myocardial infarction patients by the development of parabiosis in the atrioventricular node. Udelnov (1961) and his pupils showed very convincingly that the functional depression of the atrioventricular node occurs under the influence of potassium ions liberated in large amounts during disintegration of myocardial fibres. The views of

Lukomsky, Friedberg and Udelnov fully coincide and differ only in their formulations.

Second degree atrioventricular block occurs in 1-3 per cent of myocardial infarction cases. Like other forms of arrhythmia, partial atrioventricular block usually appears in the beginning of the disease and disappears after the end of the acute period. Sometimes partial atrioventricular block develops into a complete block. Reverse transitions also occur. Both these conduction disturbances take place in 5.3 per cent (Dolgoplosk) to 13 per cent (Eligulashvili) of myocardial infarction cases. Partial or complete atrioventricular block must be prognostically evaluated as an unfavourable sign because it is accompanied with a high mortality rate.

Complete transverse heart block occurs in myocardial infarction, according to Friedberg (1966) in 2.4 per cent of cases. Other authors report about the same findings. A final diagnosis can be made only on the basis of an electrocardiogram. Bradycardia is the most constant clinical sign of complete transverse block.

In complete atrioventricular block bradycardia is exceptionally stubborn. It does not change under the influence of either respiration, emotional stress or stimulation of the carotid sinus. Even a rise in body temperature cannot quicken the heart rate. In complete atrioventricular block the correct decelerated cardiac rhythm may now and then be disturbed by extrasystoles usually arising in the branches of the bundle of His.

Considerable diagnostic importance is attached to the periodically appearing, sharply intensified first heart sound, the so-called pistol-shot sound, the detailed and vivid description of which was made by Strazhesko (1955). It is heard during simultaneous or almost simultaneous contraction of the atria and ventricles. This sound can be heard only on prolonged auscultation because the frequency of its appearance varies considerably.

The Adams-Stokes syndrome is the most vivid, although inconstant clinical sign of a complete heart block. It is based on temporary cardiac arrest. Clinically it is manifested in loss of consciousness. The patient first grows pale, then the pallor is superseded by cyanosis, especially noticeable on the mucous membranes. When the cardiac contractions are not restored, epileptoid convulsions and often involuntary micturition and defaecation occur 15-20 sec after the cardiac arrest. After recovering consciousness the patients have absolutely no idea of what had happened to them. Such attacks of various severity and duration may follow each other over a period of one or two days. During one of these attacks the patient may die.

The Adams-Stokes syndrome most commonly arises during the transition from incomplete to complete atrioventricular block. It is usually observed in the beginning and at the end of the attacks of ectopic arrhythmias (ventricular and supraventricular tachycardia, cardiac fibrillation, and 'volleys' of polytopic extrasystoles).

Complete block appears during the acute period of infarction. It usually disappears in one or two weeks. The prognosis of this complication of myocardial infarction is very serious. Of late, owing to the wider use of new methods of controlling arrhythmia, the use of artificial cardiac pacemakers in particular, the prognosis has become more favourable.

Teodori (1956) observed disturbances in atrioventricular conduction most commonly in isolated infarctions of the interventricular septum and in patients with infarction of the anterior wall spreading to the interventricular septum. According to Friedberg (1966), disturbances in atrioventricular conduction occurred about equally frequently in infarctions of both the anterior and posterior walls of the left ventricle.

Intraventricular conduction disturbances are manifested as blocks of the branches of bundle of His or Purkinje's fibres. They usually arise during the first days of the disease. The block of the branches of bundle of His occurs the most commonly. Like other conduction disturbances, it may occur in a patient long before the infarction owing to diffuse cardiosclerosis or cicatricial changes remaining from a past infarction. Camouflaging the ECG signs of infarction it noticeably complicates its diagnosis. The block of the bundle branches combines with other cardiac rhythm disturbances and particularly frequently with disturbances in atrioventricular conduction.

The *QRS* complex exceeds 0.13 sec, according to Lukomsky (1964), in 7-9 per cent of myocardial infarction cases. If all cases of broadening of the *QRS* complex, beginning with 0.11 sec, are ascribed to these disturbances, their percentage increases to 13.2 (Ostapyuk, 1965). A stable bundle branch block occurs much more often than an intermittent block. Sometimes a bundle branch block may be the only ECG manifestation of acute myocardial infarction.

As regards prognosis bundle branch block is evaluated unequally by different authors. According to Teodori (1956) it is a diagnostic rather than a prognostic problem. Other authors consider that intraventricular conduction disturbances have an unfavourable prognostic significance. In order to prove the foregoing proposition it is necessary to evaluate the prognostic significance of intraventricular block of contingents of patients with an infarction of equal size and localization. Such studies have not been made, as far as we know. This does not warrant a final prognostic evaluation of intraventricular block.

The disturbances in cardiac rhythm described above appreciably deteriorate the prognosis. It is still unclear, however, whether a more serious prognosis is determined by arrhythmias as such or it is associated with the differences in the functional state of the circulatory system in infarction patients with arrhythmias and those with a normal rhythm.

According to Kozhevnikov (1963) arrhythmia occurs 50 per cent more often in patients with atherosclerotic cardiosclerosis than in

those without any signs of cardiosclerosis during the pre-infarction period. The higher mortality in infarctions with rhythm disturbances is possibly in some measure determined by not equal heart condition during the pre-infarction period. It must also be taken into account that the severest forms of arrhythmia usually occur in extensive infarctions. In these cases death may ensue as a result of the vastness of the infarction irrespective of the presence or absence of arrhythmia.

Personal experience warrants the assertion that the condition of a myocardial infarction patient noticeably deteriorates upon appearance not of any, but only of some disturbances in the cardiac rhythm. These include all tachycardiac arrhythmias and the transverse heart block. It should be emphasized that in myocardial infarction these cardiac rhythm disturbances are also seldom stable. They disappear relatively easily under the influence of modern methods of treatment. Even such disturbances in normal cardiac activity as fibrillation and ventricular arrest have of late ceased to be synonyms of death.

The new data on the extremely high incidence of arrhythmias in myocardial infarction show that the prognosis is determined not by a mere diagnosis of arrhythmia, but by its severity.

Syndromes due to Dynamic Disturbances in Cerebral Circulation

Cerebral circulation disturbances in myocardial infarction are usually of a dynamic character and most commonly arise during the incipient period of the disease. General cerebral and focal symptoms are distinguished in their clinical picture.

General cerebral symptoms develop as a result of a brief or more prolonged diffuse cerebral ischaemia. The general cerebral symptoms comprise nausea, vomiting, reflex intestinal paresis, dizziness, disturbance in consciousness and psychomotor excitation sometimes observed in the beginning of the disease (see Pain Syndrome).

Focal symptoms are a result of localized cerebral ischaemia which develops in connection with organic disturbances in the patency of cerebral vessels or a relative insufficiency of blood supply to the brain. The character of the clinical picture is determined by the localization and form of the vascular disturbances.

The symptoms and signs of diffuse and focal ischaemia sometimes even precede infarction. If the pain syndrome in such cases is not pronounced or cannot be revealed because of the severity of the condition, an erroneous diagnosis of syncope or cerebral stroke is made, while the myocardial infarction remains undiagnosed. Infarction patients with a clinical picture of cerebral stroke are often placed in a neurologic department.

The disturbances in cerebral circulation during myocardial infarction were studied in detail by Bogolepov who suggested that the resultant clinical picture be designated first by the term 'apop-

lectiform syndrome' and later by the term 'coronarocerebral syndrome'. Subsequently the pathogenesis and clinical aspects of this syndrome were studied by Melikova, Panchenko, Lavrentiev, Lukomsky and others.

According to Bogolepov, the coronarocerebral syndrome in the form of apoplectic strokes, coronarocerebral crises and transient phenomena of impaired cerebral circulation occurs in 12.8 per cent of myocardial infarction cases. In our experience this syndrome was observed much less frequently, i.e. in 1.3 per cent. According to Bogolepov (1949), apoplectiform and comatose states most commonly arise when the infarction is localized in the anterior wall, and, according to Gulo (1965), in the posterior wall of the left ventricle. Troshin (1961) encountered disorders of cerebral circulation during myocardial infarction in men nearly twice as often as in women.

In most patients the disturbances in cerebral circulation are manifested as a transient mild clouding of consciousness, syncope and stupor. Deep disturbances in consciousness, such as a comatose state, occur seldom. During the many years of our work in the department of internal diseases of a city hospital we observed them only twice. Diffuse cerebral ischaemia during myocardial infarction usually occurs as a result of an acute decrease in the minute volume attended with a more or less marked hypotension. It should be remembered that it may occur in normal and even elevated arterial pressure. Thus an acute decrease in the minute volume is the principal cause of its occurrence. This point of view can be supported by numerous clinical observations which established the appearance of diffuse cerebral ischaemia during attacks of paroxysmal tachycardia, cardiac fibrillation with tachysystoles and other diseases involving a decreased minute volume.

The brain is known to be more sensitive than the other organs to oxygen hunger. Acute cerebral hypoxia leads to a swelling of the nerve cells, perivascular and pericellular oedema. Autopsy reveals cerebral and meningeal oedema. Small haemorrhages and ischaemic foci are found in the brain on histological examination. A more protracted failure of cerebral circulation leads to the appearance in the cortex of nonthrombotic lesions of malacia.

In atherosclerosis of the cerebral arteries an acute decrease in the minute volume and sharp hypotension often cause focal cerebral ischaemia which is most strongly pronounced in the reservoir of the cerebral artery most strongly affected by the atherosclerotic process. The cerebral arteries, like the coronary, are functionally terminal, but in cases of sharp atherosclerosis more or less pronounced collaterals develop between their separate branches. Ischaemia of a particular part of the brain occurs not only because of its insufficient blood supply through the conducting artery, but in some measure also as a result of an insufficient collateral blood flow.

Both the diffuse and focal cerebral ischaemia develops as a result of a relatively inadequate blood supply to the brain, i.e. there is

a disparity between the requirements of the brain in blood supply and the capacity of the circulation system to meet them.

The foregoing conception of vascular failure of the brain is analogous to the generally accepted conception of coronary insufficiency. To confirm its correctness we can mention the findings of Raevskaya (1958) who reports cases of disturbances in cerebral circulation in myocardial infarction patients at the moment of a sharp fall of arterial pressure. An acute decrease in the minute volume during transient cardiac arrests is always attended with acute cerebral ischaemia. The latter can also be reproduced in experiment by occluding the arteries carrying blood to the brain (Corday *et al.*, 1949).

Tetelbaum (1960) explains the disturbances in cerebral blood supply during myocardial infarction by an increased excitability of the receptors located in the cerebral vessels, which preceded the disease. In his opinion the pain impulses arising in the heart in the beginning of myocardial infarction cause in the first place spasms of the cerebral vessels, which give rise first to syncope and then to the pain phenomena in the heart.

To be sure, in some myocardial infarction cases syncope develops first, the pains in the chest appearing a few minutes after the patient has regained consciousness. This does not, however, prove either the increased excitability of the receptors in the cerebral vessels or their involvement in the morbid process before the myocardial receptors are involved. Moreover, it is well known that a momentary loss of consciousness, which is usually diagnosed in the clinic as a syncope, is often observed in myocardial infarction either at the height of the pains or regardless of the pain syndrome.

It should also be remembered that the cerebral vessels, like those of the heart, do not take part in the homeostatic regulation of arterial pressure. The studies of Green, Kepchar and others have shown that the volume blood flow through the brain does not depend on stimulation of the sympathetic nerve. It cannot be altered either by intravenous administration of arterenol or by blocking the adrenergic nerves.

Pickering (1948) explains the transitory disturbances in cerebral circulation during cardiovascular diseases by embolisms or thromboses. We regard this hypothesis as also unsatisfactory. Strukov (1959) has shown that in myocardial infarctions embolisms occur much less frequently than signs of focal disturbances in cerebral circulation. From this it follows that in many cases the disturbances in cerebral circulation arise without any connection with embolisms, although such connection is not excluded.

A transient loss of consciousness in myocardial infarction has been described by many clinicians. The divergence between various clinical schools is not in the recognition of the possibility, but in the conception of the mechanism of its occurrence. The momentary loss of consciousness in myocardial infarction is usually diagnosed as syncope. Supposing that syncope always develops as a result

of vasomotor paresis Grotel (1940) and certain other clinicians assumed that not only the loss of consciousness, but also the fall of arterial pressure occurred in myocardial infarction under the influence of vasomotor paresis. Pain was considered the principal, if not the only, cause of syncope.

Detailed studies of the clinical aspects of myocardial infarction, and especially the use of the method of prolonged recording of electrocardiograms, made it possible to elucidate a multiplicity of causes and of mechanisms of transient loss of consciousness diagnosed in the clinic as syncope. In its general form this idea has for a long time been discussed in the Soviet clinic, but the knowledge of the mechanisms of syncopal states is still inadequate. This is not due to difficulties of reproducing these states in experiment, but to their transient character. Until recently the transitoriness of syncope was an insurmountable obstacle to studying the changes in haemodynamics. Only since the introduction into the clinic of the staining method of determining the minute volume has it become possible to investigate not only the mechanism of syncope, but also the influence on it of various procedures and medicinal substances.

It was found that in syncope arising during cardiac catheterization and after administration of hypotensors the volume of blood flowing through the brain noticeably diminishes. Studies of the character of haemodynamic changes made it possible to elucidate the main cause of the resultant cerebral ischaemia. Fick's method (Fick's principle) and the method of stain dilution enabled one to establish that during syncope the minute volume is practically unaltered. In experiments with catheterizing the right cavities of the heart it was found that the flow of venous blood to the heart all through syncope remains normal and that an increase in the rate of the venous inflow is accompanied with an adequate increase in the minute volume.

The arterial pressure in the organism is maintained at a more or less constant level owing to the perfection of the mechanisms which regulate the minute volume and vascular resistance. In cases of a sudden fall of the general peripheral resistance which occurs on opening an arteriovenous anastomosis the arterial pressure at first sharply decreases, but is soon restored to the initial level through a marked increase in the minute volume of the blood.

In the above-described forms of syncope the minute volume does not noticeably change. It follows that diffuse cerebral ischaemia in this condition occurs as a result of sharp hypotension which may be caused only by an acute fall of the general peripheral resistance. Although the loss of consciousness is a result of cerebral ischaemia, the concurrent pallor, nausea, cold and sticky sweat, involuntary urination and other symptoms arise owing to generalized stimulation of the subcortical centres of the vegetative nervous system.

The foregoing form of syncope is known in modern literature as vasodepressor (vasomotor) syncope. It often appears in response

to pain stimulation. Although the pain syndrome in myocardial infarction is usually fairly strongly pronounced the arising haemodynamic disorders are nevertheless of an entirely different character, the minute volume being, as a rule, decreased and the general peripheral resistance increased. No changes in haemodynamic characteristic of vasodepressor syncope during myocardial infarction have as yet been found.

Diffuse cerebral ischaemia in myocardial infarction sometimes develops as a result of strongly pronounced bradycardia caused by atrioventricular block. It arises occasionally during frequent ventricular extrasystoles. By means of continuous recording of electrocardiograms it was found that the loss of consciousness often occurs in myocardial infarction patients during attacks of ventricular tachycardia and in the beginning or at the end of attacks of supraventricular paroxysmal tachycardia and cardiac fibrillation. During this time transient fibrillation of the ventricles or their arrest are often observed.

In these complications of myocardial infarction diffuse cerebral ischaemia is manifested as transient losses of consciousness. It is clear that the cause of cerebral ischaemia is not the fall of the general peripheral resistance, but a complete or nearly complete failure of the pumping function of the heart.

In addition to the diffuse cerebral ischaemia signs of generalized stimulation of the vegetative nervous system appear. A clinical picture develops resembling in many respects that of the vasodepressor syncope. It is known that atherosclerosis patients often have a syndrome of increased activity of the carotid sinus. In these patients bradycardia is not always a result of transverse heart block. Sometimes it may arise reflexly in connection with elevated sensitivity of the carotid sinus receptors.

The clinical manifestations of insufficient blood supply to the brain during myocardial infarction are quite different. Their character depends to a considerable degree on whether diffuse or local ischaemia of the brain develops. In the latter case the localization of the foci is determined by the degree of stenosis of the conducting artery and the markedness of the collateral circulation. Acute circulatory failure in myocardial infarction is most commonly attended with mild mental disorders which are displayed by apathy, weakening of the memory and attention, and the absence of a critical attitude to one's own condition.

According to our observations, central pareses usually occur in the form of hemipareses with a clearly predominant affection of an arm or leg. Pure pareses of the right leg indicating an affection of Rolando's area were noted in two of our patients, and clonic spasms of the left leg associated with stimulation of the anterior central gyrus in one. Pain and temperature sensitivity on the affected limbs was decreased.

Motor aphasia characteristic of affection of Broca's area was dia-

gnosed in three of our patients. During the acute period of the disease they exhibited the features of dysarthria and stuttering. The speech became slow. In a few days these disturbances disappeared. Partial motor aphasia and sensory aphasia were observed in one patient. He had difficulties in understanding what was being said to him. His own speech was also disordered and difficult to comprehend.

Correct diagnosis of the aforesaid symptom complexes arising in connection with dynamic disturbances of cerebral circulation may prove complicated. The diagnostic difficulties increase when patients with disturbances in cerebral circulation have no pains in the chest. The difficulties become particularly great if the myocardial infarction is not accompanied with typical changes in the ECG.

In all such cases the physician's diagnostic successes are in large measure determined by his ability to collect and evaluate the anamnestic data. The information on preceding diseases, the medicines usually taken by the patient and the succession in which the different symptoms appeared must be duly taken into consideration. It is important not only to reveal the symptom, but also to detail it and appraise its vividness at the moment of its appearance and at the moment of the patient's examination, and also the character of the changes in each symptom under the influence of medicinal substances. The necessary information must be obtained not only from the patient, but also from his associates.

In the clinical picture of the disease it is sometimes possible, in addition to the symptoms that have developed as a result of affection of the brain, also to reveal the symptoms of the disease that led to the appearance of signs of failure of cerebral circulation.

The dynamic disturbances in cerebral circulation during myocardial infarction have to be most commonly differentiated from its disturbances in slowly developing thrombosis of cerebral arteries. In both cases the period of marked disturbances is often preceded by more or less transitory disorders of consciousness in the form of syncopic or semisyncopic states. An incomplete loss of consciousness is usually observed. Sometimes monopareses develop. The symptoms of focal affection of the brain in thrombosis of cerebral arteries gradually increase. Characteristic of most disturbances in cerebral circulation during myocardial infarction is their transient character. On repeated examination of the patient it is usually found that motor aphasia, disorders in the functions of the cranial nerves and pareses of the limbs do not remain invariable. Their intensity and markedness may noticeably change in the course of but a few hours.

The dynamic disturbances in cerebral circulation have to be differentiated from cerebral haemorrhage much less frequently. The latter is characterized by a sudden onset and the development of a comatose state which sometimes lasts several days. These patients

usually have a red face and stertorous respiration. Hemiplegias with an immediate fall of the muscle tonus and a decrease in tendon reflexes develop rapidly. Pathological tendon reflexes, as also Kernig's sign, usually appear in all the compared conditions.

Considerable importance should be attached to the patient's general appearance. In myocardial infarction the skin is usually pale. In severe cases the skin is cyanotic. In cerebral apoplexy the face is hyperaemic. In myocardial infarction the respiration is shallow and accelerated, in cerebral haemorrhage it is slow and in some cases stertorous. The main differences between the compared conditions are revealed by dynamic examination of the cardiovascular system.

The characteristic signs of myocardial infarction are sharply muffled heart sounds, tachycardia, increasing dyspnoea and heart failure, hypotension and appearance of characteristic changes in the ECG. In organic disturbances in cerebral circulation these signs are usually absent or show no tendency to progressive deterioration.

The ECG changes characteristic of myocardial infarction are sometimes revealed only after comparing the results of several examinations. Clinical (and this means hard) experience does not permit of diagnosing a disease on the basis of a separate symptom because the same or similar symptoms may occasionally be observed in various diseases. A diagnosis should be based not so much on the presence or absence of particular symptoms as on their markedness and mainly on their dynamics.

The diagnosis of temporary cardiac arrest can be made not only without an electrocardiogram, but even without a stethoscope. The patient suddenly loses consciousness. He stops breathing and his pulse cannot be palpated not only on the radial, but even on the carotid and femoral arteries. In a few seconds he develops cyanosis and convulsions, urinates and sometimes defaecates involuntarily. In another 15-20 sec effective cardiac contractions are restored, the patient's consciousness clears up and he can tell what happened before the attack.

The therapeutic measures at the patient's bedside during the described Adams-Stokes attack must be instituted at once. In character they coincide with those taken in cases of sudden death.

The dynamic disturbances in cerebral circulation during myocardial infarction develop not as a result of local affection of the cerebral arteries, but under the influence of disturbances in the central circulation. The clinical picture of the attendant syndromes is determined by the functional state of the circulatory system, on the one hand, and by the markedness and localization of atherosclerosis in the cerebral arteries, on the other.

The fall of perfusion pressure in shock tells in the first place on the functional state of the brain parts which receive blood through the sharply stenosed conducting artery and cannot satisfactorily

compensate for the insufficient blood supply through the major vessel because of the weak collateral blood flow.

The foregoing conception of the functional insufficiency of cerebral circulation in separate areas of the brain makes it possible to explain the reappearance of the selfsame clinical signs in myocardial infarction patients by the repeated development of cerebral ischaemia in the same area. Sufficiently strongly pronounced haemodynamic disturbances in the brain may give rise to structural changes. Correct understanding of the causes of disturbance in cerebral circulation is indispensable to a proper choice of methods of prevention and treatment.

Abdominal Syndrome

Substantial clinical material has of late been accumulated indicating that pains in the abdominal region during myocardial infarction are sometimes associated not with repercussion phenomena, but with the appearance of acute pancreatitis, erosions and acute gastro-intestinal ulcers. Particularly stubborn pains behind the sternum and in the epigastric region are observed when acute ulcers are localized in the lower part of the oesophagus, the stomach and the duodenum. Erosions and acute ulcers in the jejunum, ileum and large intestine are described much less frequently possibly because of the difficulties of their timely diagnosis.

Destructive changes in the gastro-intestinal tract usually occur during the first days of infarction. Much less frequently they develop two or four weeks later (Moiseev and Filimonova, 1969). In the stomach single or multiple erosions and ulcers are in most cases located in the lesser curvature in the region of the gastric canal and the adjacent portions of the mucosa.

Acute ulcers result from necrosis of the mucous and submucous coats of the stomach or other parts of the gastro-intestinal tract. The inflammatory process in these ulcers usually manifests itself as a round cell infiltration located on the border of the necrosis and the underlying tissues, for which reason the edges of the ulcers are usually soft. Unlike chronic gastric and duodenal ulcers the edges of the acute ulcers in the gastro-intestinal tract do not rise above the surface of the mucous membrane. The erosions and small gastric ulcers developing in a myocardial infarction patient in most cases rapidly cicatrize. The necrosis spreads to the muscular coat of the stomach or intestine much less frequently and results in perforation.

Acute erosions and ulcers are displayed in the clinic as stubborn abdominal pains, hardly relieved by narcotics, as nausea, vomiting, gastric or intestinal haemorrhages and gastric or duodenal perforations with subsequent development of peritonitis. Nausea and vomiting are observed in most of the patients. Literature does not contain any information indicating the true incidence of these signs

of myocardial infarction. According to our findings, the patients usually begin to vomit after administration of morphine and its substitutes. We observed vomiting in the very beginning of the disease only in 8 per cent of patients.

Recurrent vomiting combined with sharp tympanites suggests the presence of acute pancreatitis or partial intestinal impatency. The grave clinical picture is sometimes caused by intestinal atonia. If it is aggravated by diapedetic haemorrhage into the lumen of the gastro-intestinal tract, it is often taken for thromboembolism of one of the mesenteric arteries. The true cause of the syndrome can be elucidated only after fairly long observation. In most cases the outcome of intestinal atonia is quite favourable. Therapeutic measures in thromboembolisms of the mesenteric arteries usually prove ineffective, and continuously increasing phenomena of peritonitis develop in addition to those of paralytic ileus.

The haemorrhages from acute erosions and ulcers are often manifested by vomiting blood or 'coffee grounds'. Tarry stools are observed less frequently. In most cases the gastric haemorrhages are slight. They are displayed by the acutely developing anaemia which soon disappears. Profuse haemorrhages in myocardial infarction are rare. Haemorrhages as a direct cause of the patient's death are even rarer.

Shelagurov and Sokolov (1963), Lukomsky *et al.* (1967), and Moiseev and Tinditnik (1967) report gastric and intestinal haemorrhages which until the patient's death showed no vivid clinical signs and were accidentally discovered during autopsy.

Perforation of an acute ulcer is manifested by a clinical picture of an acute abdomen. Luckily this complication occurs seldom. During many years of our practice we observed only one case which occurred on the first day of the infarction.

Acute gastrectasis occurs in myocardial infarction still less frequently. Vasilenko and Melikova (1959) hold that gastric atonia is attended with the development of paralytic hyperaemia and haemorrhage into the stomach by way of diapedesis.

In Lazovsky's opinion (1947) acute gastric erosions and ulcers form under the influence of anoxia of the gastric wall. This opinion is confirmed by experimental and clinical findings. The rise of healthy dogs in a pressure chamber usually results in formation of acute erosions in their stomachs. Acute gastric ulcers often occur in severe heart failure, i.e. in cases of sharp anoxia of the gastro-intestinal tract.

Acute ulcers and erosions are observed not only in myocardial infarction. They sometimes appear in chronic heart failure, during therapy with steroid hormones, in burns and a number of other diseases.

Danilyak (1962) regards gastric haemorrhages as one of the manifestations of the general adaptational syndrome. According to Selye, gastroduodenal ulcerations should be considered a result of

toxic influence of histaminelike substances liberated in the organism during the alarm reaction the first phase of which is always accompanied, in addition to other changes, by a generalized decomposition of tissues, disturbance in the capillary permeability and formation of acute erosions in the gastro-intestinal tract.

Shipp *et al.* (1959), and Evdokimov *et al.* (1966) discovered increased excretion of uropepsin in some cases of myocardial infarction. It is well known that its content in the urine reflects the content of pepsinogen and hydrochloric acid in the gastric juice. The authors associate the formation of acute ulcers with the rapid increase in secretion of gastric juice and its digestive action on the gastric mucosa. They hold that the increase in gastric juice secretion in the acute period of myocardial infarction is one of the results of hyperfunction of the hypophyseal-adrenal system.

The function of this system in myocardial infarction is undoubtedly increased. Gastric erosions and acute ulcers form most commonly in infarction cases which involve a maximum strain of the organism's defensive forces, i.e. a maximum possible increase in the function of the hypophyseal-adrenal system.

While not rejecting the aforesaid facts, we merely wish to point out, on the basis of clinical experience, the necessity for a more cautious approach to the problem of causal relations between them. It is known that myocardial infarction may be aggravated by the formation of an acute gastric ulcer in a patient who had suffered from chronic achlorhydric gastritis. The formation of acute ulcers in the large intestine apparently must not be associated with the digestion of its mucosa by gastric juice (Moiseev and Tinditnik, 1967). The increased production of corticosteroids and the increased secretion of gastric juice in myocardial infarction patients must evidently be regarded as only one of the possible causes of formation of acute ulcers and erosions in them.

According to Bogolepov (1949), autopsies of people who died of cerebral haemorrhage or cerebral tumour sometimes reveal haemorrhages and erosions of the gastric and duodenal mucosa. The author associates them with the impairment of the diencephalon or the brain stem. Burdenko and Mogilnitsky provoked gastric haemorrhages, erosions and ulcers in dogs by destroying parts of the diencephalon in them. Similar results by acting on the diencephalon were obtained in experiments of the school of Speransky who regarded them as standard forms of dystrophies.

The mechanisms whose activity led in these cases to the formation of acute gastric ulcers and erosions merit more detailed study.

Physiologists discover in the intestinal vessels a large number of adrenergic receptors, mainly vasoconstrictive. Cholinergic vasodilatative receptors are found in the intestines in rather moderate numbers. Stimulation of the sympathetic nerve and intra-arterial administration of adrenalin or noradrenalin appreciably alter the capacity of the vascular bed of the intestines. These findings war-

rant the assumption that the intestines take an active part in the homeostatic regulation of circulation.

As was already pointed out, acute circulatory failure in myocardial infarction is always attended with centralization of circulation with the bulk of the blood directed to the vitally important organs. The vasomotor tonus of the abdominal organs increases immediately after occlusion of the coronary artery (Kyanzhuntseva, 1966). The studies carried out by Lewis and Mellander (1962), Lillehei *et al.* (1964) and others show that circulatory centralization occurs during any acute fall of the minute volume irrespective of its cause and that two stages or phases can be distinguished in this adaptive reaction.

At first there is a constriction of arterioles of the gastro-intestinal organs accompanied with an increased vasomotion of metarterioles and precapillary sphincters, their hyper-reactivity to small doses of adrenalin. In this period (which corresponds to the 'tension collapse' of the old authors) the abdominal organs are in a state of ischaemic anoxia.

In later stages of haemorrhagic collapse the vasomotor activity is as if paralysed, i.e. the arterioles and veins dilatate and their active vasomotion ceases, owing to which blood is deposited and sequestered in the small intestinal vessels. Stagnant anoxia of the tissues ('relaxation collapse' of the old authors) develops. It is assumed that at this stage capillary permeability sharply increases, intravascular aggregation of blood cells occurs, and interstitial oedema of tissues and, in severe cases, haemorrhages into the intestinal wall take place.

In evaluating these data clinically it is necessary to take into consideration that haemorrhagic collapse and collapse in myocardial infarction differ from each other not only in causes, but also in the mechanisms of their occurrence. The obturator mechanism in the liver of dogs is much more strongly pronounced than it is in man, therefore the character of circulatory disturbances in the abdominal cavity of dogs apparently in some measure differs from that of man. Moreover, in man the homeostatic regulation of circulation is effected with the necessary participation of the cerebral cortex, the inhibition in which even in severe collapse does not usually reach the depth that it always does in the anaesthetized animal.

It is believed that the changes in the peripheral resistance during homeostatic regulation of arterial pressure are effected essentially through the adrenal-sympathetic system. In the beginning of myocardial infarction signs indicating excitation of the sympathetic nervous system usually predominate. Its hyperfunction is also observed in chronic heart failure which also involves a redistribution of the minute volume. The bulk of it is diverted to the brain and heart. The blood flow through other organs decreases absolutely and relatively with the result that in patients with chronic heart failure, like in those with acute circulatory failure, in severe cases erosions

and acute ulcers in the stomach and the small intestine are often formed. The clinical picture of the abdominal syndrome in chronic heart failure does not in any way differ from that of acute myocardial infarction.

In discussing the problem of protective and compensatory mechanisms Bykov and Kurtsin (1960) conclude that the protective-compensatory and protective-adaptive functions are subordinated to the central mechanisms and are controlled by them.

The adaptive redistribution of the minute volume in a normal organism is always rather transitory phenomenon. In myocardial infarction the redistribution mechanism of the reduced minute volume is turned on for a longer period. In severe cases of myocardial infarction vasoconstriction develops simultaneously in several organs and reaches such an intensity that never occurs in a healthy organism. It follows that in extent, force and duration the adaptive reaction in a myocardial infarction patient noticeably differs from that in a normal organism.

The increase in intensity and duration of the normal adaptive reactions in the organism leads to a state where these reactions, as Parin (1960) put it, often grow to be dangerous to the organism and in fact become pathological reactions. The reason for the change of physiological reactions to pathological cannot apparently be understood without due regard for the role of the higher parts of the central nervous system whose regulatory influences effect the coordination of individual links of the compensatory-adaptive processes in the organism.

There is as yet no single point of view on the mechanism of vascular complications during the acute period of myocardial infarction. At the present level of knowledge in this field it can only be assumed that in addition to the disturbances in the trophic function of the central nervous system, a certain role in their occurrence is played by a disturbance in the homeostatic regulation of circulation.

The clinical picture of the abdominal syndrome in a myocardial infarction patient forms under the influence of a number of factors. Today the role of each of them is estimated mainly on the basis of clinical observation.

Correct evaluation of the pain sensations in the abdominal cavity is of a considerable practical importance. To avoid serious diagnostic mistakes the physician must be skilful in collecting and evaluating the anamnesis and be well versed in the clinical picture and peculiarities of the course not only of myocardial infarction, but also of certain other diseases. Owing to the development of the abdominal syndrome and irradiation of pains to the epigastric region the clinical picture in some cases of infarction resembles very much that of an acute abdomen. In rare cases an acute abdomen may really develop. The appearance of the abdominal pains demands the physician's close attention and in all cases indicates the need of watching the patient over a long period of time.

5

COMPLICATIONS

Cardiac Aneurysm and Thromboendocarditis

Thinning of a part of a cardiac wall with formation of a pulsating bulging is called aneurysm. In most cases it arises acutely and usually becomes chronic. Until recently practising physicians had little knowledge of the clinical picture of this complication of myocardial infarction. Before World War I autopsy data were published on 300 cases of cardiac aneurysm. It was diagnosed while the patients were still alive in only two cases. As late as 1945 White considered an intravital diagnosis of cardiac aneurysm to be impossible. Now owing mainly to Soviet researchers the clinical picture has been studied in sufficient detail. According to Lukomsky (1963), cardiac aneurysm is diagnosed intravitally in 75-80 per cent of cases.

One of the first descriptions of the clinical picture of cardiac aneurysm was made in 1896 by Kazem-Bek, a Kazan professor. Subsequently the clinical picture of this complication was described by Yakovlev (1927), Glazova (1949), Volynsky (1949), Nesterov (1954), Tokareva (1959), Raevskaya (1960), and others; their findings indicate that cardiac aneurysm is most commonly a complication of myocardial infarction. It usually forms in the acute period of infarction when the necrotized part of the cardiac wall begins to dilatate and bulge during systole under the increased intraventricular pressure and during diastole under the pressure of the blood flowing in from the atrium.

Necrotized myocardium is the only wall of the aneurysm in the acute period of the disease. Subsequently connective tissue begins to develop in the necrotic zone and the acute aneurysm becomes chronic.

Cardiac aneurysm forms less frequently for the first time in the subacute period of infarction and even during more remote periods.

In these cases the aneurysm forms by dilatation of the young and yet weak scar or by bulging in the region of the old scar. This apparently occurs as a result of a formation of small necrotic foci around the old scar, which merge and from an annular zone of muscular tissue of decreased resistance. Subsequently this zone begins to bulge together with the old scar during systole.

Nesterov *et al.* (1963) have described 'functional muscular' aneurysms. In these cases the dilatated wall of the aneurysm consists of muscle fibres in a state of dystrophy. The small necrotic foci are arranged separately and do not merge into a continuous cicatricial field.

The recent studies have not confirmed the opinion of the old authors on the exceptional rarity of cardiac aneurysms. According to the findings of modern authors (Volynsky, 1949; Nesterov, 1958, and Tokareva, 1959) this complication develops in 20-40 per cent of myocardial infarction patients. Aneurysms form particularly often in transmural infarctions. It was long since noted that the more extensive the myocardial infarction the more often it is aggravated by aneurysm. Its formation is accelerated under the influence of the circumstances fostering an increase in intraventricular pressure which is particularly dangerous in the acute period of infarction.

The experimental studies carried out by Kipshidze (1957), Tokareva (1960) and Dikareva (1964) have convincingly demonstrated that a physical load during the acute period of infarction fosters formation of aneurysmal bulging of the myocardium. Clinical experience also indicates that strict bedrest during the first days of the disease is conducive to a more favourable course of infarction. Strict bedrest does not prevent the development of an aneurysm in transmural myocardial infarction, but failure to observe a sparing regimen may lead to the development of an aneurysm even in cases of a less extensive infarction and may apparently exert an unfavourable influence only through a change in intraventricular pressure.

Volynsky and Dadashvili note that among patients with aneurysms those with elevated arterial pressure prevail. This fact is corroborated by Kogan (1958) who holds that an aneurysm forms mainly because the patient retains high arterial pressure even after the onset of infarction. The extensiveness of the myocardial infarction and the high intraventricular pressure of which it is possible to judge in the clinic (although very approximately and inaccurately) are, in our opinion, the main factors contributing to the development of cardiac aneurysms.

Aneurysms are most commonly located (50-75 per cent of cases) on the anterolateral wall of the left ventricle and about one-third as often on the posterior surface or apex of the heart. Other localizations are encountered very seldom. The following aneurysms are distinguished: diffuse with a gentle bulging of the external contour and a scyphoid depression from inside the heart, saccular and fun-

giform. Only diffuse aneurysms may be relatively stable. The other types tend to grow with dilatation of the wall.

The aneurysmal cavity is in most cases filled with thrombotic masses. Under the influence of blood pressure the thrombi become laminated. They gradually flatten out and become cup-shaped with the hollow in the centre. Fresh thrombi tending to embolism may form in the cavity of the cup.

In 70-80 per cent of cases cardiac aneurysms are complicated by thromboendocarditis. According to Panfilov (1961), a parietal thrombus forms on the first day or even in the first hours of the disease. Its occurrence is fostered by a disturbance in the integrity of the endocardium, on the one hand, and general disturbances in circulation and the biochemical properties of the blood, on the other. Once formed the thrombus closely adheres to the aneurysmal wall. The latter consists at first of dead muscle fibres which are gradually replaced by connective tissue with many elastic fibres.

The aneurysmal wall and the thrombus located in the aneurysm sometimes undergo calcification. In most cases calcinosis is localized in the aneurysmal wall and borders the latter as a thin linear shadow either on top or on a side. Sometimes it occurs without an aneurysm in which case it assumes diagnostic importance as a true sign of survived myocardial infarction. The aneurysmal wall often adheres to the pericardium, which favours its strengthening.

Wide employment of electrocardiographic, roentgenokymographic and electrokymographic methods of examination have appreciably improved the diagnosis of aneurysms. Large aneurysms located on the anterolateral surface or in the region of the apex of the heart are now confidently diagnosed in most hospitals. The experience of Soviet surgeons shows that we have now met with another aspect of the problem, i.e. with an overestimation of the results of physical and instrumental methods of examination which resulted in hyperdiagnosis of aneurysms (in 22.4 per cent of cases according to Petrovsky, 1961).

The development of surgical techniques and equipment makes it possible in a number of cases to resect cardiac aneurysms successfully. For this purpose it is necessary to know before the operation not only that the patient has an aneurysm, but also its size, shape and localization, and the functional state of the heart muscle because the condition of the patient who survived a myocardial infarction is determined, according to Karpova's findings (1966), not by the presence or absence of a cardiac aneurysm, but by the state of the contractile function of the preserved myocardium.

A vast myocardial infarction complicated by an aneurysm takes in many cases an unfavourable course usually with the appearance of clinical picture of acute heart failure one or two months after its onset.

According to Kozlov, Yurenev and Kalinina, hypertension of the lesser circulation with an increase of pressure in the pulmon-

ary artery of up to 80/30 mm Hg is often found in patients with left ventricular aneurysms. Morphological studies of the lungs have shown that pulmonary hypertension in these patients has features of postcapillary hypertension whose characteristic signs are stenosis of the pulmonary venules and arterioles because of hypertrophy of the muscular elements of their walls and sclerosis of inner coat. Relative mitral insufficiency, hypertrophy of the right ventricle and of the walls of the pulmonary artery are found at the same time.

Dikareva established by her studies that in cardiac aneurysm the hypertrophy of muscle fibres develops successively first in the wall of the right ventricle, then in the interventricular septum and, lastly, in the aneurysmal wall. In the light of these findings the appearance of ECG and X-ray signs of hypertrophy of the right ventricle after myocardial infarction must apparently be taken as an indirect indication of a possible development of a ventricular aneurysm.

Depending on the severity of the affection and the effectiveness of treatment pulmonary hypertension either persists and leads to the formation of the so-called second barrier or disappears and appears only under a physical load which is usually accompanied with dyspnoea and attacks of cardiac asthma. In cases of an unfavourable course the patient develops a clinical picture of total heart failure. Myogenic dilatation of the left ventricle becomes the cause of relative mitral insufficiency.

In its compensation and decompensation mechanisms an aneurysm very much resembles mitral heart disease. This resemblance gave Nesterov the right to speak of mitralization of cardiac aneurysm 'which usually occurs during a protracted course of the disease'. It should be taken into account, however, that the cardiac mitralization syndrome is also observed in infarction of the papillary muscles and other extensive infarctions of the left ventricle.

Cardiac aneurysms usually occur in combination with thromboendocarditis. Intravital diagnosis of this complication is possible, but in most cases is very difficult. We have observed protracted fever of irregular type which does not disappear after administration of antibiotics, prolonged persistence of leucocytosis and an accelerated ESR only in two-thirds of thromboendocarditis cases. In one-third of the cases this complication occurred with normal body temperature. In some thromboendocarditis cases the leucocyte count remained normal all through the course of the disease, confirming the opinion of Nesterov and Dikareva of a possible latent course of thromboendocarditis.

Embolisms in internal organs may be used for diagnosing thromboendocarditis only in cases where other sources of embolic material cannot be found except thrombophlebitis of the pelvic organs and the lower extremities. Embolisms in the organs of the systemic circulation occur in about two-thirds of cases during the first two or three weeks of the disease, i.e. in the period when the thrombotic

masses have not become organized and may easily break away from the parietal thrombus.

According to Kazem-Bek (1896), a characteristic sign of an aneurysm is a disparity between the increased pulsation in the region of the cardiac apex and a small pulse on the radial artery. The diagnostic importance of this sign was later confirmed by Yakovlev (1927), Nezlin (1956) and others. Lukomsky (1967) also considers a decrease in the pulse arterial pressure to be one of the important symptoms of cardiac aneurysm.

Many authors indicate that pulsation in the third-fourth intercostal space left of the sternum is the earliest and most reliable sign of cardiac aneurysm. We found in many cases that pulsation in this region appeared in anterolateral myocardial infarction on the first day and was easily traced during the subsequent three or five days. In many postinfarctional autopsies we were unable to discover either aneurysms or a thinning of the left ventricular wall. Precordial pulsation occurred in these cases apparently owing to the bulging of a part of the heart muscle that had lost its resistance and adjoined the anterior thoracic wall.

Clinical experience indicates that aneurysm of the left ventricle may cause pathological pulsation in the precordial region, but pulsation of a part of the anterior thoracic wall in a myocardial infarction patient is not always a result of the formation of cardiac aneurysm. It may merely indicate an anterolateral localization of the infarction.

According to some authors, the apical impulse in patients with cardiac aneurysm is usually intensified, while the heart sounds are weakened. We found weakened heart sounds only in patients with third degree heart failure. In all the other cases the heart sounds remained clear. A protodiastolic gallop rhythm is auscultated in about one-half of the patients. A weakened first sound usually also persists in the late period of the disease. An intensified second sound over the pulmonary artery is apparently due to the development of pulmonary hypertension.

In our opinion, the diagnostic role of murmur in cardiac aneurysm is often overrated. The presystolic murmur in this complication was first described by Kazem-Bek (1896). Gertsen (1966) noted that in cardiac aneurysm presystolic murmur, unlike that in mitral stenosis, is combined not with an intensified, but with a weakened first sound. Diastolic murmur was auscultated only in two of our 50 patients. Systolic murmur in cardiac aneurysm is recorded much more frequently. The reason for it is a relative mitral insufficiency due in some cases to an affection of the papillary muscles and in others to myogenic dilatation of the heart.

Percussion always determines dilatation of the heart, but it is of no particular diagnostic importance because dilatation of the heart is observed after any extensive myocardial infarction complicated by heart failure.

Aneurysms of the apex and the posterior wall of the left ventricle are much harder to diagnose because of the absence of the pathological pulsation in the anterior thoracic wall.

An aneurysm located at the heart apex leads to the appearance of a double apical impulse; the first wave of the impulse occurs at the end of diastole and the second wave is the apical impulse (Nesterov).

The ECG changes in cardiac aneurysm were studied by many clinicians. Some of them (Nezlin, Dolgoplosk, Zenzinov, and others) insist on the existence of specific ECG changes characteristic only of aneurysm, while others (Volynsky, Raevskaya, Lukomsky, and others) hold that there are no ECG changes pathognomonic for aneurysm. Clinical experience confirms the latter point of view.

The ECG changes in cardiac aneurysm do not differ in any way from those recorded in old myocardial infarction of the same localization. The arciform rise in the *S-T* segment developing into a negative *T* wave is considered characteristic. The *S-T* interval increases as a result of transmission of the cavity potentials through the fibrous wall of the aneurysm.

An inversion of the *T* wave is usually observed in at least three chest leads and is combined with deformation of the *QRS* complex to a *QS* (which is considered particularly characteristic) or *QR* form. Aneurysms of the posterior wall of the left ventricle show deep *Q* waves in the second and third leads and an elevated *S-T* segment developing into a negative *T* wave.

The foregoing changes in the ECG may persist for several years. With the development of mitralization of the heart its electric axis turns right and a small R_1 wave and deep S_2 and S_3 waves appear on the ECG. A block of the left branch of the bundle of His is often observed. The ECG results make it possible, if not to establish, at least to suspect cardiac aneurysm.

The results of radiography are of a much greater diagnostic importance, in our opinion, although not all authors share this opinion. Anterolateral and apical aneurysms can be revealed by the limited bulging on the contour of the left ventricle. In cases of fairly large aneurysms located on the posterior wall of the left ventricle the passage of barium through the oesophagus becomes difficult or there is a displacement of the oesophagus (Ivanitskaya, 1950). An aneurysm is seen particularly well in cases of calcification of its wall.

Radiokymography and electrokymography enable paradoxical pulsation of an aneurysm to be determined. When the aneurysmal cavity is filled with a large thrombus closely adhering to the ventricular wall the pulsation of the heart contour is sharply weakened and may even be completely absent. An aneurysm is appreciably more frequently revealed by radioscopy with the use of an image converter and subsequent radiocinematography of the heart. It is necessary to look through the different films shot in a rectangular,

first and second anterior oblique projections. This method makes it possible, much more frequently than the other methods, to discover paradoxical pulsation on various parts of the heart contour.

To reveal aneurysms, a method of scanning the heart is being proposed of late, but aneurysms can be diagnosed best of all by using cineangiocardiography of the left ventricle, which enables one not only to reveal an aneurysm, but also objectively to estimate an extent to which it is filled with blood during systole and diastole.

The observations carried out by Nesterov, Kolobutina, Dodashvili, and others, indicate that patients with cardiac aneurysms live as long as those with postinfarctional cardiosclerosis. They die most commonly of progressive heart failure or recurrent myocardial infarctions. Death from embolism occurs in about half the number of cases.

Methods of surgical treatment of aneurysms have been developed of late (Petrovsky, 1960).

Thromboembolisms

Prior to the extensive introduction of anticoagulants and later fibrinolytic substances into the treatment of myocardial infarction thromboembolisms were one of the widespread complications that considerably aggravated the course of this disease and often served as the cause of death. The percentage of these complications varied, according to different authors, between 13-14 (Teodori, 1956; Konyaev, 1959, and Raevskaya, 1964) and 25-30 (Lenègre and Gerbaux, 1952, and Wright *et al.*, 1954). These rather important differences could have been due not only to the composition of the patients, their selection in the particular clinics, but also to some peculiarities of the therapy (even without due regard for the use of anticoagulants). More extensive use of medicines for treating heart diseases, for example, reduces the incidence of circulatory failure and favours a decrease in the tendency toward thromboembolic complications. Anticoagulants changed the picture of myocardial infarction as concerns its incidence and the severity of thromboembolisms but have not eliminated completely these complications. Thromboembolic complications may arise even on a background of massive treatment with anticoagulants and a corresponding level of blood prothrombin (to say nothing of the cases where the use of anticoagulants is contra-indicated). According to Lukomsky and Kazmina (1961, 1963, 1967), with the use of anticoagulants thromboembolisms of various vascular regions in connection with myocardial infarction occurred in 5.6 per cent of cases. McCohr and Sampson observed almost the same incidence in 500 patients given sufficient doses of anticoagulants. In our 400 patients such complications amounted to about 2 per cent, which we associate with an earlier and wider use of fibrinolytic agents.

It is interesting to note that Pollard *et al.* (1962) reported the

occurrence of thromboembolic complications in nine patients on a background of haemorrhagic phenomena caused by administration of anticoagulants. These data not only indicate that the problem of thromboembolic complications in myocardial infarction is still urgent, but also confirm the opinion that the mechanisms of thrombus formation have not been completely revealed.

Today the ideas of the pathogenesis of thromboembolic complications are much broader and deeper than they were, for example, ten or fifteen years ago. Detailed studies of the coagulant properties of the blood and the appearance of new information on the anticoagulation system (Kudryashov, 1960) not only extended our ideas of this process, but also favoured the elaboration of new methods of treatment. In this work we are not dwelling on the complex mechanism of thrombogenesis dealt with in sufficient detail in special monographs (Kudryashov, 1960; Markosian, 1960; Chazov, 1966, and others). It is only necessary to point out the important role played by the disturbances in the anticoagulation system in the occurrence of thromboembolic complications during myocardial infarction.

It is known that the patient's organism reacts to the threat of thrombogenesis with an increase in the anticoagulant and fibrinolytic properties of the blood. On how adequate the developing reaction will be depends whether a thrombus will form in each particular case. Our studies and those of our collaborators (Nikolaeva, Kozhevnikova, Ananchenko, Mazur), and also the latest studies of a number of other authors (Bazazian, Ermilov, Panchenko, Yanushkevichus and Bluzhas, and others), show that the occurrence of thrombosis in atherosclerosis, which, as a rule, is present in myocardial infarction, is a result not only of an increased content of coagulants in the blood, but also of the depression of the anticoagulant mechanisms. For example, in patients at early stages of atherosclerosis a more strongly pronounced anticoagulation reaction is observed at the height of an angina pectoris attack (manifested, in particular, in an increased heparin content) than in patients with severe forms of the disease. We therefore consider thrombosis in atherosclerosis not only from the point of view of morphological changes in the vessels, but in the first place from that of the functional disturbances. Functional peculiarities, in particular those of the anticoagulation reaction, play an important role in the occurrence of thromboembolic complications during myocardial infarction.

It is interesting to note that the variety of pathoanatomic findings (coronary thrombosis, parietal thrombosis, thromboembolic complications) in myocardial infarction in some measure correspond to the differences in the biochemical changes found in the acute period of the disease. In the first place an increased heparin content and fibrinolytic activity of the blood are revealed during the first days of the disease in a large number of myocardial infarc-

tion patients which reflect the general patterns of the defensive anticoagulation reaction. This increase is particularly large in cases with a strongly pronounced pain syndrome. In shock this reaction on the contrary is most commonly absent. The tendency toward thromboembolic complications and thrombogenesis becomes clear. The regular pattern of changes in some of the anticoagulant mechanisms during myocardial infarction discovered by us is also confirmed by a number of authors (Belli *et al.*, 1962; Ermilov, 1962; Nikolaeva, 1962; Konyaev *et al.*, 1964, and others).

The absence of thrombi in the coronary vessels and other vascular regions in a certain percentage of myocardial infarction cases (according to some data, up to 30 per cent) may be due to the defensive anticoagulation reaction. True, in most cases it is not sufficient to prevent thrombosis, although it helps to limit the process. The reaction of enhancing the anticoagulant and fibrinolytic properties of the blood during myocardial infarction is, however, transitory and disappears already on the second, less frequently on the third, day, sometimes being superseded by depression of the anticoagulant mechanisms. But, if we take into account that in myocardial infarction, an increased content of blood coagulants persists for a long time: antihaemophilic globulin (Ilyushina and Kudryashov, 1963), factor VII (Poller, 1957; Malyarovsky, 1961; Panchenko, 1962), fibrinogen (Fradkina, 1956; Kozhevnikova and Andreenko, 1964; Konyaev *et al.* 1964, and others) the tendency toward thromboembolic complications and thromboses on the third or seventh day of the disease becomes clear. But recent works on thromboses more often contain a fallacious, in our opinion, tendency to ignore completely the local changes as a factor conducive to the appearance of this pathological process.

At the same time it is known that the local changes not only contribute to the appearance of rough surfaces on which formed elements of the blood (of the source of some coagulants) settle down and break up more easily, but also cause biochemical and physico-chemical changes in the vessel wall, thus increasing, in a definite area, the tendency toward thrombogenesis. We can point out, in particular, the changes in the bioelectric potential in connection with atherosclerotic changes, the increased thromboplastic activity in the areas affected with atherosclerosis, the decreased number of heparinocytes in them, the decrease in fibrinolytic activity, etc. As regards the pathogenesis of thromboembolisms it is necessary specially to emphasize the importance of vasospasm in the occurrence of this complication.

The significance of local changes in myocardial infarction particularly emphasized in cases of intracardiac thrombosis which is the main source of thromboembolisms. Intracardiac thrombosis is a frequent finding in myocardial infarction. According to Konyaev, (1959), a parietal thrombosis in the heart cavities was found in 43 per cent of the 400 fatal myocardial infarction cases. Of the 45 pa-

tients who had died of myocardial infarction complicated by thromboembolisms in the systemic circulation Raevskaya (1960) did not find intracardiac thrombosis only in 16.

According to our own autopsy findings (92 cases) thrombosis in the heart cavities in myocardial infarction was found in 26 per cent. We associate the rarity of parietal thrombosis, as also of thromboembolic complications, with the extensive use of anticoagulants and fibrinolytic agents. The most favourable conditions for the formation of an intracardiac thrombus are created in cases of complication of myocardial infarction by an aneurysm and in the so-called protracted forms of the disease. At the Institute of Cardiology Olenina observed 13 patients operated on for cardiac aneurysm connected with myocardial infarction. Despite the administration of anticoagulants and fibrinolytic substances thrombi were found in the aneurysmal sac in four patients. Certain authors report on the development of thrombosis in acute or chronic postinfarctional aneurysms (Shestakov, Latushni, Ton Tan, Shapiro and Olivetti, and others). It is very difficult to diagnose intracardiac thrombosis in connection with myocardial infarction. Only indirect signs of the development of parietal thrombosis can be indicated. Such suspicions arise in cases where the course of myocardial infarction is complicated by endocarditis. A severe, protracted course of the disease with a long persisting leucocytosis, an accelerated ESR, subfebrile temperature, circulatory failure hardly amenable to treatment with cardiac glycosides, tachycardia, copious nocturnal sweating, the appearance of a coarse systolic murmur at the apex—all these symptoms must put the physician on his guard as regards a possible addition of an intracardiac thrombosis to the myocardial infarction. If cardiac aneurysm is found the suspicion of an intracardiac thrombosis increases and becomes a certainty in the presence of thromboembolic complications. Subsequently during activization of a patient it is necessary to remember the possibility of an X-ray diagnosis of an intracardiac thrombosis (change in the character of the radiokymogram waves, retraction of the heart contours in the region of the thrombus, etc.). We suggested using radioactive fibrinolysin for diagnosing thrombosis (Chazov and Bogolyubov). Radioactive fibrinolysin is tropic to thrombus and usually concentrates in its region. This creates the conditions for diagnosing thrombi not only by the clearance of radioactive fibrinolysin removal, but also directly by scanning the heart.

In myocardial infarction thromboembolic complications may also occur without intracardiac thrombosis, but most thromboembolisms develop in connection with thrombotic processes in the heart cavities.

One of the most frequent and severe complications of myocardial infarction is thromboembolisms of the pulmonary artery and its branches. The urgency of this problem is determined not only by the severity of the complication which considerably deteriorates

both the coronary and general circulation, but also by the diagnostic difficulties, especially on a background of myocardial infarction. In the development of pulmonary thromboembolisms it is necessary to indicate the role of thrombophlebitis of the legs and of the small pelvis, and the importance of the sclerotic and inflammatory changes in the pulmonary artery (Kushelevsky and Schmidt, 1958; Raevskaya, 1960; Pavlov, 1962, and others). Pulmonary thromboembolisms considerably deteriorate the prognosis of myocardial infarction (Staemmler and Wilhelms, 1953; Naegeli, 1960; Perlik, 1964, and others). This complication is particularly dangerous for people over the age of 50 in whom, moreover, it occurs much more frequently. It should be emphasized that in myocardial infarction we did not observe the regularity noted by Votchal and Magazanik (1959) and other authors, namely, that in 90 per cent of the cases thromboembolism was combined with circulatory failure. Often a thromboembolism of the pulmonary artery (but most probably its thrombus) occurred in the first hours of the myocardial infarction in the absence of any signs of circulatory failure. We are inclined to think that primary thrombosis of the pulmonary artery is of greater pathogenetic importance. The general conditions for thrombogenesis may lead not only to the development of coronary thrombosis, but simultaneously, in the presence of local changes in the pulmonary artery, contribute to the development of thrombosis also in this region. In an experiment we managed, by changing the animal's functional state (increasing the tendency toward spasm) and raising the thrombogenic properties of the blood (by administering thrombin) on a background of lipoidosis, not only to produce thrombi in the cardiac vessels, but also to observe the development of a typical pulmonary infarction.

The problem of thromboses and embolisms of the pulmonary artery is at once important and diagnostically difficult. Even without myocardial infarction such thromboembolic complications are diagnosed not more than in 40 per cent of patients (Panchenko, 1964; Perlik, 1964, and Zlochevsky, 1965) and the difficulties the physician experiences at the patient's bedside are therefore understandable. They are also determined by the peculiarities of the clinical picture which depends on the calibre of the affected vessel and the extent of the thromboembolic process. According to some authors, in 10 per cent of cases it is embolism of the large trunks of the pulmonary artery, while in 75-80 per cent vessels of medium calibre are affected, and it is this that makes the difference in the clinical picture. A number of characteristic symptoms of pulmonary embolism (pain in the chest, the appearance of signs of acute circulatory failure, changes in the blood and the ECG) can often be adequately explained by the course of the main pathological process, but medical observation and intuition are frequently the only method of diagnosing the complications. As for the evaluation of the various symptoms of the disease, Perlik, for example, considers a

sudden appearance of marked dyspnoea and tachycardia to be the first and characteristic sign of pulmonary thromboembolism. In discussing the symptoms of this complication of myocardial infarction it is necessary to proceed from its pathophysiologic characteristics. Pulmonary thrombosis or embolism leads, first of all, to a sharp increase in pressure in the pulmonary circulation, a reflex spasm of the pulmonary vessels and a decrease in their capacity. These changes cause, in turn, an overstrain of the right ventricle, reducing the delivery of blood to the left ventricle and, consequently, to the systemic circulation and the coronary vessels. It is for this reason that a sudden deterioration of the condition of the myocardial infarction patient attended with signs of circulatory failure of various degrees is often the main sign of pulmonary thromboembolism. Thus Sasahara *et al.* (1966) observed cardiac decompensation in two-thirds of the patients with pulmonary thromboembolism.

Attempts are often made to judge about pulmonary thromboembolism by the appearance of pains in the chest. Far from always occurring in thromboembolism the pain syndrome (35-40 per cent of cases) is still less demonstrative in a myocardial infarction patient in whom pain may often be connected with the main pathology. Haemoptysis appears in pulmonary thromboembolism still less frequently than pains in the chest (Raevskaya, 1960; Tareev, 1951, and Krol *et al.*, 1967).

Of the general symptoms characteristic of pulmonary thromboembolism mention must be made of a frequent rise in temperature and leucocytosis.

Radiographic examination of the lungs in myocardial infarction is extremely difficult because it is usually limited to an X-ray picture with a patient in a recumbent position. Scanty as they usually are the X-ray symptoms (clearance of the pulmonary fields, asymmetry of the roots of the lungs, rarely occurring darkening of pulmonary tissue) are poorly revealed in radiography performed under such conditions.

Electrocardiography offers much more. As early as 1935 McGrinn and White noted in pulmonary thromboembolism the appearance of an increased S wave in lead I and Q wave with a negative T in lead III. Besides, the occurrence of pulmonary thrombosis or embolism may be attended with an increase in P wave in leads I and III. The difficulties of evaluating the ECG picture in thromboembolism of the pulmonary artery and its branches are associated with the fact that in this complication coronary disturbances may arise both reflex and those connected with general haemodynamic changes. This pertains, in particular, to the appearance of a negative T wave and displacement of the ST segment. Sometimes a suddenly appearing bundle-branch block may serve as a sign of thromboembolism. Unlike the ECG picture of myocardial infarction, the characteristic sign of ECG changes associated with pulmonary thromboembolism is their considerable lability. As for differential dia-

gnosis, mention may be made of an increase in the S wave in lead I or in leads I and II simultaneously with type Q_3-T_3 changes. ECG changes in pulmonary thromboembolism appear only in cases of occlusion of a relatively large branch of the pulmonary artery or in affection of a sufficiently large number of its small branches. It is for this reason that there may be no ECG changes in 10-40 per cent of cases.

In recent years the attention of researchers is attracted by the possibility of using enzymes for differential diagnosis. Such possibilities are less in studying the content of transaminases, which increases both in myocardial infarction and pulmonary thromboembolism. Other enzymatic systems are much more demonstrative.

At the Institute of Cardiology Nekrasova (1962) found an increase in the content of transaminases only in half the cases of pulmonary thromboembolism. Like Peterson (1959) and other authors, she attaches much greater importance to determination of the aldolase content. The peculiarities of the changes in these two enzymes during pulmonary infarction make it possible to use their correlation to some extent for differentiating them from coronary disturbances. An increase in transaminases is more characteristic of changes in the myocardium, while high aldolase figures are typical of pulmonary thromboembolism with subsequent infarction. However, today there cannot as yet be a question of 'enzymatic' diagnosis of pulmonary thromboembolism and pulmonary infarction, especially if they occur on a background of myocardial infarction. This is hindered by the non-specific character of the 'enzymatic' reactions in inflammations and necroses. Other criteria associated with changes in the content of enzymes are being sought. For example, after analysing the changes in blood enzymes of 100 patients with pulmonary thromboembolism Tremblay and Sasahara (1966) consider an increase in lactic dehydrogenase with normal transaminases to be the most specific. Today we are attaching considerable importance to studying the iso-enzymes of lactic dehydrogenase for differential diagnosis of the affections of the heart and lungs. These studies conducted in our clinic by Smirnov were based on the difference in the spectrum of lactic dehydrogenase iso-enzymes in cardiac and pulmonary tissue. It was natural to assume that the spectrum of iso-enzymes in the blood would change depending on the localization of the focus of affection. Clinical findings confirmed these assumptions.

The diagnostic difficulties and the absence of a strict specificity of the syndromes and laboratory changes account for the continuous quest for new diagnostic methods in pulmonary thromboembolism. It goes without saying that the method of angiography of the pulmonary vessels recommended by some authors is rather dangerous in cases where pulmonary thromboembolism develops during myocardial infarction. Of much greater interest are the attempts to study

the state of the pulmonary circulation by means of radioactive isotopes.

The search of radioactive isotopes for diagnosing pulmonary thromboembolism is now being conducted in two main directions. One of them is based on studying the possibilities of using the well-known radioactive substances, e.g. tracer albumin, and the state of pulmonary circulation. The other direction suggested in 1963-1964 by our collaborators (particularly the series of studies carried out by Bogolyubov) and us is based on the use of radioactive fibrinolysin. We utilized the property of fibrinolysin, administered from without, to concentrate in the region of the thrombus. Determination of the site of the greatest concentration of radioactive fibrinolysin helps to locate the thrombus. Moreover, it turned out that in thrombosis the radioactive fibrinolysin disappears from the blood several times as fast as it does from that of healthy people. It stands to reason that we cannot as yet recommend extensive utilization of radioactive isotopes for diagnosing pulmonary thromboembolism. There is no doubt, however, that a valuable and safe method of determining pulmonary thrombosis may be elaborated in the future.

In conclusion we must emphasize the difficulties of diagnosing pulmonary thromboembolism in myocardial infarction and the necessity of thoroughly analysing the complex of subjective, objective and laboratory criteria of this severe complication.

Second to pulmonary thromboembolism in frequency and importance are affections of the abdominal aorta and the arteries of the lower extremities. The principal role in the occurrence of these complications is played by intracardiac thrombosis which often aggravates the course of myocardial infarction. Raevskaya (1960) reports that of the 70 myocardial infarction patients in whom the course of the disease was aggravated by thromboembolism of various vessels the aorta and peripheral vessels were affected in 24 (one-third of all cases). It should be emphasized that in the development of this pathological process during myocardial infarction an important role is played not only by the character of the intracardiac changes and the development of intracardiac thrombosis, but also a number of general (depression of the anticoagulant mechanisms) and local factors.

The degree of the development of collateral connections plays an important part in thromboembolism of the abdominal aorta, and particularly the peripheral vessels. We know of cases where the thrombus or embolus was found only by arteriography some time after the myocardial infarction patient had recovered. Naturally in these cases there was no characteristic clinical picture.

In most cases, however, this complication develops acutely and has characteristic symptoms which enables the character of the affection to be determined rather easily. To be sure, the zone of the affection, as also the severity of the process, depends on how fast

the artery was occluded since a slow development of thrombosis creates conditions for development of collateral circulation. As a rule, the 32 cases of thromboembolism of the abdominal aorta and the peripheral arterial trunks observed by us (27 of these patients had survived myocardial infarction) were characterized by an acute onset of the disease—acute pains in the leg, pallor of the skin and disappearance of arterial pulsation. In about half the number of such cases this beginning is accompanied with an acute cardiovascular failure and sometimes by severe collapse. Moreover, if we consider the results of circulatory disturbances in the leg as ischaemia and subsequent tissue necrosis, we shall get an idea of the severity of this complication which considerably affects the course of myocardial infarction. This is why before the era of extensive use of vasodilatative and fibrinolytic substances thromboembolism of the aorta and the peripheral arteries was one of the most important causes of fatal results of myocardial infarction. The development of gangrene and intoxication often compel the physician to consider an amputation of the limb, the performance of which during the acute period of myocardial infarction is fraught with severe consequences, although it is the only chance of success.

Of late thromboembolism of the renal arteries in myocardial infarctions has become a relatively frequent pathology. Of 70 myocardial infarction patients with thromboembolic complications Raevskaya found thrombosis of the renal arteries in 21. According to certain data, the renal arteries are second to the pulmonary vessels as regards embolism found on autopsy (14.5 per cent). As in the affection of the aorta and the peripheral arteries, atherosclerotic changes play an important role in the development of thromboembolism of the renal arteries. They contribute to the development of thrombosis which accompanies embolism, determine the development of collaterals, etc. The severity of the arising complication is determined by the possible occurrence of shock during the acute period of embolism, and disorders in circulation in which not unimportant part is played by a marked increase in arterial pressure in connection with renal ischaemia. In addition to the appearance of such symptoms as pain, changes in the blood, and elevated temperature, changes in the urine and an increase in arterial pressure may be distinguished in the clinical picture of this complication of myocardial infarction. Thromboembolism of the renal arteries is characterized by a pain syndrome of various intensity often attended with oliguria and vomiting. Pains in the abdominal cavity, in addition to which there may be leucocytosis, an accelerated ESR and raised temperature, simulate acute catastrophes in the abdominal cavity and attacks of nephrolithiasis. Thromboembolism of renal arteries is also characterized by an absence of pain irradiation. The urinary syndrome is mainly determined by an increased permeability of the walls of small vessels, owing to which erythrocytes and protein appear in the urine. The specific gravity of the urine does not change,

as well as the excretory function of the kidneys is not disturbed. Oliguria must be taken into consideration in differential diagnosis. An increased arterial pressure is not a necessary symptom of renal thromboembolism, but it is often present and is of differential diagnostic importance. The absolute signs of affection of the renal arteries are determined outside the acute period of myocardial infarction when the regime is extended and it becomes possible to carry out urologic, radiologic and radiographic examinations. Chromocystoscopy and intravenous urography reveal a picture of a 'mute kidney'. Renography with intravenously injected radioactive sodium iodohippurate makes it possible to reveal either a difficulty of its passage into the kidney or a total block of the renal artery. Correspondingly there is no characteristic rise in the curve, which is present in that of the other, intact kidney.

It should be emphasized that in a number of cases of renal thromboembolism there is no characteristic picture and the complication appears as vague pains in the abdomen and the small of the back, as nephrolithiasis, etc. Autopsy therefore often reveals small sections of necrosis in kidneys or old scars which were not diagnosed intravitally as thromboembolism.

Much greater difficulties arise as regards diagnosis and treatment of thromboembolism of mesenterial vessels. This most common complication of myocardial infarction deteriorates the prognosis because the treatment is limited to administration of fibrinolytic preparations which are of little effect in these cases. At least in none of our 14 cases did we produce any effect by administering fibrinolysin with heparin or heparin with streptokinase. In these cases even early diagnosis does not affect the prognosis because surgical intervention during the acute period of myocardial infarction is impossible in view of the severity of the disease. In the development of thromboembolism of mesenterial arteries a certain role is played, not only by the embolism, particularly in connection with intracardiac thrombosis, but also by the atherosclerotic changes in these vessels (according to Isserson and Ropinson). These authors found such changes in 10 of 51 cases of thromboembolism of mesenterial arteries. Vasospasm is of a certain importance in the pathogenesis of this complication. It is precisely by this functional factor that we explain the appearance of the precursors of thrombosis in the form of abdominal pains resembling the 'pre-infarctional' state in patients with angina pectoris.

In its clinical picture thromboembolism of the mesenterial arteries may resemble any acute catastrophe in the abdominal cavity, and it is for this reason that correct diagnosis ranges from 30 to 50 per cent.

The onset of the disease is usually acute, although, as we have pointed out, in a number of cases it may be preceded by attacks of abdominal pains of an indefinite character. During the first hours of the disease the pains are extremely intense, an indefinite locali-

zation being their distinctive feature. At first the abdomen is soft and is felt in a limited part. Rather soon, however, meteorism and tension of the abdominal wall appear. The Shchotkin-Blumberg's sign is exhibited by about half the number of patients. Of the 14 patients under our observation the occurrence of thromboembolism of mesenterial arteries was accompanied with a severe collapse. In most cases there is constipation as a result of intestinal paresis. The characteristic symptoms of thromboembolism of the mesenterial arteries is a doughy swelling palpated between the navel and pubis; Raevskaya explains it by an accumulation of blood in the intestinal loops. In this complication of myocardial infarction there are frequent haemorrhagic phenomena.

Thromboembolism is a frequent cause of the disturbances in cerebral circulation during myocardial infarction. From the internists' point of view, however, they present considerable diagnostic difficulties and are usually studied by neuropathologists. At the same time the appearance of fibrinolytic substances calls for the early differential diagnosis of thromboembolism, dynamic disturbances in cerebral circulation and haemorrhage. This problem on which depends not only the pathological process in the brain, but also the very life of the patient must be solved by internists and neuropathologists.

Ruptures of the Heart

Cardiac ruptures were first described by Harvey in 1647, and the clinical picture of external ruptures with cardiac tamponade in 1798 by Knopf, a St. Petersburg physician. There are external ruptures when the blood effuses into the pericardial cavity, and internal when a shunt is formed between the left and right ventricles. The internal ruptures also include ruptures of papillary muscles.

According to our findings, and those reported by Glazova (1949), Vakhurkina (1949), Zolotova-Kostomarova (1950), Tapitser, Shamesova (1956), Lukomsky and Tareev (1958), and Vilkovyssky and his associates (1965), covering autopsies of 4762 myocardial infarction cases cardiac ruptures were found in 301 (6.3 per cent). Similar data were reported by foreign authors. This complication is the direct cause of death from myocardial infarction about twice as often.

External ruptures occur five to ten times as often as internal. The rupture usually looks like a lacerated wound and is most commonly located on the anterior surface of the left ventricle. Ruptures of the posterior wall of the left ventricle occur 50-67 per cent less frequently, while those of the lateral wall are a fairly rare complication of myocardial infarction. Rupture of the atria is encountered still less frequently. Ruptures of the interventricular septum occur much more frequently than avulsion of the papillary muscles.

As is known, women have myocardial infarction less frequently than men, but, according to McQuay *et al.* (1955) ruptures in them

are observed as often as in men (according to Moiseev (1962), Gefter and Matusova (1962), and Vilkovyssky *et al.* (1965), even more often than in men). The statistical data of the foregoing authors must not be overrated because they were not standardized according to age.

Cardiac ruptures are most commonly observed in patients over the age of 60 and rarely in persons under 40. The average age of women suffering from myocardial infarction is noticeably higher than that of men. The foregoing facts are now considered firmly established. They warrant the assumption that the differences in the incidence of cardiac ruptures between men and women are determined by the unequal age of the patients.

According to Vakhurkina (1949), cardiac ruptures usually occur in the period of the most strongly pronounced phenomena of myomalacia cordis, their appearance depending on the rate of the development of myocardial necrosis. Most commonly it happens in the first and sometimes the second week of the disease. Cardiac ruptures developing in later periods of infarction are extremely rare. In 10 of the 14 patients under our observation they took place in the first week, in five of them on the first day of the disease. Ruptures most commonly occur in primary myocardial infarction apparently in virtue of the insufficient development of collateral circulation in these cases.

Myomalacia is undoubtedly the principal cause of cardiac rupture. Many authors point out the higher incidence of ruptures in patients with arterial hypertension. Persistence of high intraventricular pressure after myocardial infarction particularly predisposes to cardiac ruptures (Glazova, Kogan). The correctness of this assumption was convincingly demonstrated by Gorokhovsky (1964). According to the material collected by him, cardiac ruptures occurred in 40 of 1070 patients with the hypertensive vascular disease and only in 32 of 1585 patients with normal arterial pressure. Patients with marked postinfarctional hypotension are less susceptible to ruptures. In the opinion of many clinicians, physical and emotional stress is one of the most important factors contributive to ruptures. Moiseev (1962) noticed that ruptures most commonly occurred during waking hours. A certain role in their occurrence is also considered to be played by failure to observe the heart-sparing regimen in the acute period of the disease.

In evaluating these data it is necessary to remember that a strict bed regimen does not always prevent ruptures and that this complication was not noted in a single patient subjected to 'therapy in an armchair' (Levine, cited by Plotz). Physical strain is probably an important, but not the only, factor that contributes to cardiac ruptures. Recent studies have shown that administration of anticoagulants does not affect their incidence.

As far back as the end of the 18th century Knopf noted that rupture is preceded by an appreciable increase in, and intensification

of, retrosternal pains and that at the moment of the rupture the patient loses consciousness. Death often occurs instantly owing to reflex cardiac arrest (Fokht, 1901; and Chernigovsky, 1943). If the patient survives the moment of blood effusion into the pericardium, a clinical picture of shock is revealed. After regaining consciousness the patient observed by Knopf was pale, his brow was covered with cold sweat, his lips were blue and his pulse was slow, soft and hardly perceptible.

After cardiac rupture the patient lives but a few minutes, less frequently a few hours. In the latter case the patient develops cyanosis of the face, which gradually spreads all over the body, and a swelling of cervical veins and other signs of acutely developing cardiac tamponade are observed. However, a dilation of the heart is revealed very rarely. Gorokhovsky discovered it only in 10 of 72 patients.

Intravital diagnosis of rupture of the heart can be made only in cases where a protracted anginous condition of an elderly patient with a transmural myocardial infarction terminates in syncope with a subsequent development of shock and signs of acute cardiac tamponade.

A rupture of the interventricular septum was diagnosed in the Soviet Union for the first time by Shvarts (1944). In the available literature we managed to find descriptions of 39 cases of intravital diagnosis of this complication of myocardial infarction.

Rupture of the interventricular septum occurs in about 0.5 per cent of myocardial infarction patients. It takes place in the same periods as external rupture, i.e. in the periods of the maximum myomalacia. The ruptures are usually located in the muscular part of the interventricular septum, closer to the apex of the heart. Soviet clinicians have made a detailed study of this complication of myocardial infarction, and it is now in many cases diagnosed intravitally. This is favoured to a considerable extent by the fact that rupture of the interventricular septum is often compatible with a more or less prolonged life of the patient.

The clinical picture of rupture of the septum resembles to some extent that of external rupture. On a background of usually intense pains in the precordial region attack of unconsciousness occurs which is followed by the development of a clinical picture of shock.

The acute change for the worse is at first most commonly taken to be a recurrent myocardial infarction. Less frequently it is regarded as a postinfarctional syndrome. If the patient survives the period of rupture, he develops a characteristic picture of an acute defect of the interventricular septum. The usual grave picture of left ventricular infarction is now combined with a right heart failure.

In the beginning the heart failure is manifested by intense pains in the right hypochondrium due to a rapid swelling of the liver. A coarse systolic murmur and systolic fremitus of the chest wall

appear. The systolic murmur is best recorded in the left third-fifth intercostal spaces near the sternum. It is clearly auscultated in the interscapular space and is conducted to the left axilla and to the right of the sternum, sometimes to the right axilla. Now and then a diastolic murmur is auscultated, indicating a passage of blood not only from left to right, but also from right to left. The signs of right ventricular failure increase with each passing day, while those of left ventricular failure (if there were any) decrease.

Many authors attach considerable diagnostic importance to disturbances in atrioventricular and intraventricular conduction but in rupture of the interventricular septum this sign is not often observed. We were unable to find it in any of our patients. Much greater diagnostic importance should be attached to the rapidly developing turn of the electric axis of the heart to the right, but this ECG sign can be revealed only in patients remaining alive for two or three days after the rupture of the septum.

The clinical picture of rupture of the papillary muscles in the early period of myocardial infarction is characterized by signs of left ventricular failure. A syndrome of steadily increasing pulmonary oedema, despite the treatment, was always accompanied with rupture of the papillary muscles in all our patients.

Signs of left ventricular failure were also noted in most of the cases described by other authors. The clinical picture of marked left ventricular failure is a background, as it were, on which another constant factor of rupture of the papillary muscles, i.e. shock, suddenly develops.

We have quite often observed a combination of shock and left ventricular failure in unfavourable cases of infarction of the papillary muscles without their rupture. The acutely arising mitral insufficiency with a simultaneous functional failure of the myocardium of the left ventricle must apparently be considered the cause of the irrepressible increase in pulmonary oedema in these affections of the heart.

In general opinion, the appearance of coarse systolic murmur in the precordial region is the most specific sign of rupture of the papillary muscles. It is believed that this symptom appears simultaneously with shock or several hours prior to it. In myocardial infarction involving the papillary muscles we did not always manage to auscultate a murmur over the cardiac region apparently because of the sharply weakened contractile properties of the myocardium. It is not impossible that in some cases it is not detected because of the patient's sudden death occurring in cardiac rupture.

The systolic murmur which sometimes resembles that of pericardial friction appears first over the apex of the heart or, being auscultated over the entire precordial region, has its maximum over the apex. Unlike the murmur arising in rupture of the interventricular septum, the systolic murmur in rupture of the papillary muscles is not attended with intense fremitus in the precordial region.

It is well heard over the whole cardiac region, but is not conducted to the right of the sternum.

Study of five of our own cases of rupture of the interventricular septum, and of literary data, has convinced us that complications of myocardial infarction under discussion sharply differ from each other also in the subsequent course of the disease.

In cases of rupture of the papillary muscles the patients do not usually live more than 24 hours after the appearance of signs of shock. Rupture of the interventricular septum in myocardial infarction is also aggravated by shock, but in these cases it is often compatible with a longer period of life. According to the materials of our clinic, in cases of rupture of the interventricular septum the patients lived for a period of up to six days after the diagnosis was established. A female patient described by Bagdasarov *et al.* (1955) lived for eight days. Starobinets and Vetchinkina (1948) reported a case where the patient had lived for seven years.

Rupture of the interventricular septum is usually not attended with a steady increase in the signs of left ventricular failure which is characteristic of rupture of the papillary muscles. On the contrary, in the cases under our observation, as well as those described by other authors, if the patients survived the moment of the catastrophe, they exhibited a more or less rapid increase in signs of right ventricular failure (the enlarged liver and the appearance of oedema on the shanks).

Some authors point out the significance of the ECG method for differential diagnosis, emphasizing frequent conduction disturbances in ruptures of the interventricular septum. A disturbed conduction observed in one of our cases of rupture of the papillary muscles indicates the unreliability of this criterion of differential diagnosis of the myocardial infarction complications under consideration.

Postinfarctional Syndrome

The causal relationship between the affection of the pericardium and angina pectoris was first discovered by Kernig in 1882. A circumscribed (usually early) and diffuse pericarditis are now distinguished in myocardial infarction.

Circumscribed pericarditis occurs simultaneously with transmural myocardial infarction and is called pericarditis epistenocardiaca, diffuse pericarditis is the main sign of the postinfarctional syndrome which sometimes develops several days or weeks after the occurrence of the infarction.

The true incidence of pericarditis in myocardial infarction is still unknown. Pathologists find traces of pericarditis in 30-80 per cent of those who died of myocardial infarction. In the clinic this complication is found much less frequently, only in 1-10 per cent cases (Chambers, 1946). In order to determine the cause of such a

marked difference Gerke (1950) studied very extensive clinical and autopsy material. He took into consideration all changes in the pericardium and found them in 83 per cent of people who had had myocardial infarction.

Pericardial adhesions are apparently not always a result of infarction. They may also develop under the influence of other diseases. Gerke's figures are probably exaggerated and give an incorrect idea of the incidence of pericarditis in myocardial infarction. Clinical data on the incidence of this complication are undoubtedly understated. The reason for it is that in pericarditis epistenocardiaca there are few symptoms.

According to Plotz (1961), early pericarditis (epistenocardiaca) is always painless. Volynsky and Gogin (1964) admit that pain in pericarditis epistenocardiaca is possible, but hold that it is impossible to distinguish this pain from that occurring in myocardial infarction. Lukomsky and Tareev (1958) point out that in the beginning of myocardial infarction pain usually lasts one or two hours, very seldom about 24 hours. Later patients with uncomplicated myocardial infarction have no longer intense pains, but a sense of pressure in the chest. If the pain persists more than 24 hours and its intensity depends on phases of respiration, it is most likely due not to myocardial infarction, but to pericarditis. Pericarditis is characterized by continuous or recurrent pain found behind the sternum, in the interscapular space and in the neck, which does not spread to the arms.

Personal experience nevertheless shows that friction murmur is often the only reliable sign of pericarditis epistenocardiaca. It appears usually on the second or fourth day of the disease and is auscultated over a period of several hours. It is often impossible to discover it even on daily examination of the patient. It is most commonly auscultated in the zone of absolute cardiac dullness. In the first days of myocardial infarction the friction murmur is always delicate; it is never loud or diffuse.

Pericarditis epistenocardiaca does not noticeably change the course of myocardial infarction, therefore many foreign clinicians hold that it has no independent clinical significance. It usually appears in transmural myocardial infarctions which run a more severe course than microfocal or subendocardial infarctions. We regard as more correct the point of view of most Soviet clinicians who, following Kernig, consider the appearance of friction murmur of pericarditis to be an unfavourable prognostic sign of infarction.

In some cases pericarditis is limited to the zone of necrosis of the muscle, while in other cases it spreads beyond it. The inflammatory process may affect the whole pericardium in which case its friction murmur is clearly auscultated throughout the precordial region even if the infarction is localized on the posterior wall of the heart. In early pericarditis it persists for one or two days after which it disappears without leaving a trace. The absence of relapses is

considered to be the most characteristic sign of this form of pericarditis.

The appearance of pericarditis which spreads beyond the necrotic zone is accompanied with ECG changes, which are described in detail by Barnes *et al.* (1932).

A concordant rise in the *RST* complex in standard leads I and III and often II is considered characteristic. A rise in the *RST* is occasionally noted only in leads I-II, while in lead III this segment remains on the isoelectric line (Lukomsky, 1943). In pericarditis the *S-T* interval is not only elevated, but is also concave or remains horizontal.

In 1904 Kernig described a patient in whom pericarditis epistenocardiaca was aggravated by exudative pleurisy. Volynsky and Gogin (1964) noticed in a number of cases a protracted course of early (diffuse) pericarditis and its tendency to relapse. They consider this form as transitional between pericarditis epistenocardiaca and diffuse pericarditis which is a part of the postinfarctional syndrome.

The main clinical signs of this pericarditis do not fundamentally differ from clinical characteristics of the postinfarctional syndrome. It is quite natural to regard the appearance of diffuse pericarditis in the first days of the disease as an earlier, than usual, manifestation of the postinfarctional syndrome.

The appearance of friction murmur in this form of pericarditis is usually accompanied with a rise in temperature and an increase in leucocytosis. Pains in the cardiac region reappear, which are constant and persist for two or three days. On subsequent days they begin to abate owing to the formation of exudate which, by accumulating in the pericardial cavity, muffles the heart sounds. At the same time the pericardial friction murmur disappears and the voltage of the ECG waves diminishes. In severer cases the cervical veins swell out and the liver is enlarged.

In typical cases the postinfarctional syndrome is as if a second disease that joins the myocardial infarction two to five weeks after its beginning. Its clinical picture was first described by Dressler in 1955. Later it was studied in detail by Damir and Sidorovich (1961), Dubrovskaya (1968), Semenovich (1969) and other Soviet and foreign authors.

Dressler (1959) diagnosed the postinfarctional syndrome in 3 per cent of myocardial infarction cases. Matusova and her associates (1965) found it in 21 of 496 patients, i.e. in about 4 per cent of cases. The clinical picture comprises pains of various intensity in the chest and protracted, usually relapsing fever developing as a result of affection of the pericardium, pleura, pulmonary tissue and (seldom) the synovial membranes by the inflammatory process.

Pericarditis is considered the main sign of the syndrome. It usually arises in the third or fourth week of the disease, sometimes earlier. In such cases it is necessary to distinguish it from limited

pericarditis epistenocardiaca. The latter, as was already pointed out, is of no independent clinical significance and is often painless.

The onset of pericarditis in a patient with the postinfarctional syndrome is usually attended with fever and always pain in the chest. Limited pericarditis epistenocardiaca, figuratively speaking, dies before it has had time to flourish (is nipped in the bud), its indistinct signs disappearing in one or two days. Pericarditis in a patient with the postinfarctional syndrome is always diffuse. Its characteristic feature is a relapsing and sometimes very protracted course. In one of the cases described by Raevskaya and Kozmina (1962) several relapses of pericarditis were observed in the course of six months.

The friction murmur of pericarditis is auscultated in about 60 per cent of patients with the postinfarctional syndrome (Matusova *et al.*, 1965). It persists from several days to a few weeks after which it begins gradually to subside owing to the abatement of the inflammatory phenomena or accumulation of exudate in the pericardial cavity. The exudate is often of a haemorrhagic character, but may also be serous (Gerke, 1950).

Pericarditis is apparently the main cause of pain in the precordial region observed in the postinfarctional syndrome. The pain is sometimes so intense that it impels the physician to think of a recurrent myocardial infarction. In strongly pronounced cases the pain is localized in the precordial region and spreads to the interscapular region up to the neck and the shoulder joints, sometimes irradiating to the abdomen. Unlike the pain in myocardial infarction, that in pericarditis becomes more intense during deep inhalations and does not spread along the arms. In some cases pericarditis does not occur alone, but is combined with pleurisy and pneumonia.

In the postinfarctional syndrome pleurisy occurs as often as pericarditis. It may be dry (in which case a friction murmur of the pleura is auscultated) or exudative in which the friction murmur of the pleura is auscultated only in the early period of its development. Left-sided pleurisy occurs more often, bilateral less frequently and right-sided very rarely. Haemorrhagic or serous exudate accumulates in small amounts, but in some patients it forms in large amounts, and repeated punctures must be resorted to.

Pneumonia occurs in about one-third of the postinfarctional syndrome cases, i.e. much less frequently than do pericarditis and pleurisy. The foci of inflammation, single or multiple, are most commonly found in the lower lobes of the lungs. The sputum sometimes contains blood, which may lead to an erroneous diagnosis of pulmonary infarction. Antibiotics do not affect the course of pneumonia.

Affections of the joints in the form of arthralgia and synovitis develop, as a rule, later than the main components of the postinfarctional syndrome. According to Artemiev and Komarova (1965), pains in the periosteum of the ribs, arthralgias, hyperaemia and

swelling around the affected joints develop in some cases on a background of pleuropericarditis and in others after its disappearance.

Isolated affections of the synovial membranes of the sternocostal joints are sometimes observed. This complication described under the name of syndrome of the anterior thoracic wall (Prinzmetal, Massumi) is displayed by parasternal pains, which noticeably increase on raising the arms or on pressing on the sternum and the sternocostal joints. Artemiev and Komarova (1965), who described in detail these forms of the postinfarctional syndrome marked by few symptoms, point out that they are characterized by relapses with periodic exacerbations and remissions.

The development of the aforesaid affections of the internal organs and joints are usually accompanied with a febrile reaction. In pleuropericarditis the body temperature may rise to 38-39 °C, but most commonly it persists at subfebrile figures. Antibiotics do not affect the fever, which usually disappears immediately after administration of glucocorticoids. The pains cease simultaneously with the fever. Suspension of corticoid hormones or a rapid decrease in their dose results in a relapse of the fever and pains. Each relapse lasts from one or two weeks to three months. According to Dressler (1955), this relapse usually develops four or six days and sometimes one or two years after suspension of the preparation.

A postinfarctional syndrome usually involves moderate or marked leucocytosis. Eosinophilia is found only in half the cases. In most cases there are no ECG changes characteristic of pericarditis, but repeated electrocardiography of the patient is necessary in order to exclude a fresh myocardial infarction. In the form of the syndrome characterized by only few symptoms there are no ECG changes. In the postinfarctional syndrome the activity of transaminases changes irregularly. C-reactive protein appears in the blood serum of about half the patients.

Most clinicians regard the postinfarctional syndrome as a kind of a second disease that develops in myocardial infarction in response to the sensitization of the organism by the antigens which enter the blood from the necrotized heart muscle.

Fatenkov (1964), Vinogradsky (1968), and others have found that anticardial antibodies appear in the blood of the myocardial infarction patient about a week after the beginning of the disease. Over a period of two or three weeks their titre gradually increases; during convalescence it gradually decreases.

Gradual cessation of antibody production is probably due to liquidation of the pathological process in the myocardium (Pletitsyn and Averiyanova, 1967). Anticardial antibodies are found in the blood not only of myocardial infarction patients, but also in about half the patients suffering from ischaemic heart disease with attacks of angina pectoris (Zhuravlev and Schmidt, 1968) and even in the blood of clinically healthy people (Semenov, 1964).

In generalizing these data Martynov and Bilynskaya (1967) con-

clude that circulating anticardial antibodies are the result of a damage to the myocardium and that their appearance indicates a vigorous activity of the mechanism which helps the organism to get rid itself of the products of myocardial disintegration.

The titre dynamics of anticardial antibodies in patients with the postinfarctional syndrome turned out to be analogous to those in myocardial infarction patients. In examining the same patients Semenovich (1969) found that the onset of the postinfarctional syndrome is accompanied either with a transient disappearance of the circulating anticardial antibodies or by a decrease in their titre. Simultaneously the histamine and serotonin blood content increases (Yurenev and Semenovich, 1970).

Subsequently the titres of anticardial antibodies of the blood begin to increase again. The eosinophil count of the blood increases and hyperglobulinaemia develop. In many patients with the postinfarctional syndrome it is possible to find delayed hyperergic reactions which are marked by positive intracutaneous tests with an antigen from a necrotized portion of the myocardium and a positive blastotransformation reaction. Administration of corticosteroids leads to the abatement of clinical manifestations of the postinfarctional syndrome and the disappearance of the circulating anticardial antibodies.

In generalizing the foregoing facts Krylov and Gordienko (1966), Semenovich (1969) and others assume that in some cases of infarction the anticardial antibodies are found not only on necrotized, but also on normal myocardial cells which they injure. The thus arising auto-aggressive process becomes the cause of the development of the postinfarctional syndrome (Semenovich, 1969) or recurrent myocardial infarctions (Vinogradsky, 1968).

Without denying the pathogenic significance of anticardial antibodies we should merely like to call attention to the fact that clinical studies determine circulating antibodies, i.e. the group of antibodies which are the effect rather than the cause of the pathological process (Ioffe, 1963). In all fatal myocardial infarction cases auto-antibodies were found only in the necrotized portions of the heart muscle and never in the normal parts of the myocardium or pericardium (Volynsky and Gordienko, 1967; and Semenovich, 1969).

Numerous researchers have not yet given any direct evidence in favour of the auto-immune origin of the postinfarctional syndrome and have not established the capacity of the circulating antibodies to injure the myocardium in experiments with a passive transmission of a disease. Until such evidence is produced the discovery of circulating anticardial antibodies in myocardial infarction should apparently be evaluated as a secondary immunogenic phenomenon indicating the markedness of a defensive immune reaction rather than the aetiology of the syndrome.

A clinical picture identical with the postinfarctional syndrome sometimes arises after a mitral commissurotomy. As the data were

accumulated it was found that for the postcommissurotomy syndrome to develop intervention on the heart itself is not obligatory. A pericardiotomy alone suffices. It is assumed that this syndrome arises as a hyperergic reaction to the blood that enters the pericardial cavity after pericardiotomy. By the analogy with this Dressler (1959) holds that in the postinfarctional syndrome pericarditis develops under the influence of the haemorrhagic exudate that forms in the pericardium in pericarditis epistenocardiaca. This point of view satisfactorily explains the onset of pericarditis in transmural infarctions, but cannot explain the cause of their development in limited myocardial infarctions.

In practical work it is often necessary to differentiate the postinfarctional syndrome from recurrent myocardial infarction and pulmonary infarctions with perifocal pneumonia. Most commonly recurrent myocardial infarction has to be excluded in a patient with the postinfarctional syndrome.

In differentiating these diseases special importance should be attached to the aforementioned peculiarities of the pain syndrome and the results of the repeated electrocardiography. In the postinfarctional syndrome the ECG signs indicating the appearance of new foci of necrosis in the myocardium are not found. The postinfarctional syndrome is characterized by persistence of fever and pericardial friction murmur for a long time, and involvement in the process of the pleura, lungs and synovial membranes. The ineffectiveness of antibiotics is also characteristic. Rapid disappearance of pain, the fever and other clinical signs of the disease one or two days after administration of steroid hormones confirms the diagnosis of the postinfarctional syndrome. It is confirmed completely by a relapse soon after suspension of the steroid hormones.

In the clinic of internal diseases pains in the region of the scapuloclavicular joints and hands occur quite often. About 90 per cent of these cases are based on a direct affection of periarticular tissues. In these cases examination reveals ossifying tendovaginitis, bursitis, inflammatory affection of the joints, capsules and tendon sheaths. Radiographs often show a focal or diffuse osteoporosis of the carpus and the head of the humerus. In about 10 per cent of cases a similar picture is found in patients without any signs of primary affection of periarticular tissues. Such cases are referred to as the development of a shoulder syndrome or a shoulder-hand syndrome (Copeman, 1969).

The main signs of this syndrome comprise limited mobility in the shoulder joint because of the more or less strongly pronounced pains which are usually constant. Sometimes they appreciably increase at night. The affections may be both unilateral and bilateral. Sometimes in addition to pains in the shoulders there are also pains in the forearms and wrists. The vasomotor disturbances arising in these cases may lead to diffuse oedema of the wrists and difficulty of movement in the wrist joints.

In three to six months the aforesaid symptoms and signs of the disease disappear either of themselves or under the influence of treatment. Less frequently the disease by continuously progressing leads to the atrophy of the skin, and the connective tissues and muscles of the shoulder and fingers with the development of contractures.

The shoulder syndrome is observed in 10-15 per cent of patients who have survived myocardial infarction. It usually arises during convalescence, but may develop three or four months after the beginning of the disease. Exactly the same syndrome is sometimes observed after disturbance in cerebral circulation and pericarditis. The aetiology of the syndrome has not as yet been established. Klimenko (1965) and certain other authors regard it as a 'second variety of the postinfarctional syndrome'. It is difficult to agree with this assertion because most cases of the shoulder syndrome reveal sign of scapuloclavicular arthrosis and ankylosing shoulder arthritis.

In these cases the shoulder syndrome is most likely a result of the development of a preceding arthritis or other primary affections of periarticular tissues.

In the opinion of Artemiev and Komarova (1965), Dubrovskaya (1968), and others, the shoulder-hand syndrome in a myocardial infarction patient is one of the manifestations of neurodystrophic disturbances that occur in connection with the main disease. The shoulder syndrome in a patient with disturbances in cerebral circulation is probably a result of direct disorders of the trophic functions of the central nervous system, whereas in patients with myocardial infarction and pericarditis it is caused by reflex influences issuing from the affected organ. The stream of impulses spreading centripetally excites corresponding segments of the spinal cord and cerebrospinal ganglia. A disturbance in their function becomes the cause of the foregoing vasomotor and trophic disorders naturally appearing in the upper extremities in this syndrome.

Constant pains lead to limited movement in the left shoulder joint which in its turn causes a moderate osteoporosis of the head of the humerus and the scapula. Long after myocardial infarction Bogolepov and his associates (1966) revealed a cardiobrachial syndrome in 30 per cent of cases. It is displayed clinically by motor and neurovascular disturbances, mainly in the left arm, changes in muscle tone, occasionally rigidity and a tendency toward contracture in the shoulder joint, a thinning of the shoulder muscles, an increase or decrease in tendon and periosteal reflexes, reflex spasm and dilatation of the vessels, and changes in skin temperature.

Protracted Course and Recurrent Myocardial Infarction

In uncomplicated cases myocardial infarction is a monocyclic disease. Myocardial necrosis first arises, then, from the third day of the disease, a leucocyte infiltration develops and a process of resorption of necrotized tissue. At the same time new connective

tissue forms in the injured zone of the myocardium. Subsequently the processes of necrosis resorption gradually subside and in the foreground processes of maturation of the newly-formed connective tissue develop in which it is always possible to find more or less extensive areas of necrotized muscle fibres.

The duration of their persistence inside the forming postinfarctional scar depends on the extent of the infarction and the coronary atherosclerosis. According to Yankevichute (1967), necrotized muscle fibres are found in the scar tissue over a period of two to four months. Subsequently they disappear undergoing hyalinosis and the so-called acellular sclerosis.

The extent of the reparation processes of infarction depends on the patient's age and the functional state of the collateral circulation. The leucocytic infiltration of the necrotized myocardium in marked coronary stenosis is negligible. In these cases the reparation of the infarction is slowed down with the result that foci of necrotized muscle fibres are sometimes found in the myocardium even six months after the appearance of the infarction.

In accordance with the character of morphological changes in the heart muscle Glazova (1956) believes it expedient to distinguish a period of acute infarction of about two weeks' duration and a period of consolidation which, depending on the extent of the infarction, lasts from one to three months.

In the period of acute infarction processes of necrosis and myomalacia prevail in the myocardium. Signs of acute heart failure and aseptic inflammation of the heart muscle predominate in the clinical picture of the disease. A postinfarctional scar forms in the period of consolidation, the aseptic inflammation gradually subsides, leucocyte count becomes normal; the ESR gradually slows down and the signs of heart failure disappear.

The succession of phenomena described above is a rough scheme. The extent of leucocyte infiltration, the rate of resorption of necrotized elements, the severity of heart failure and the character of disturbances of the other cardiac functions depend on the concomitant diseases, the extent of coronary failure and the organism's reactivity.

In 1938 Fogelson noticed that in some cases myocardial infarction ran as a relapsing infectious disease. Somewhat later Grotel (1940) reported that the febrile period of myocardial infarction may last three or four weeks. Lukomsky pointed out the possibility of a still more protracted acceleration of the ESR in myocardial infarction.

In 1951 Shestakov described myocardial infarctions whose characteristic clinical sign was a tendency toward a protracted course with recurrent rises in body temperature and a periodic appearance of leucocytosis. Somewhat later this form of myocardial infarction was studied in detail by Chernyshova (1953), Gvatua (1957) and other scientists.

It has now been established that a protracted course of myocardial infarction is most common in patients with marked coronary atherosclerosis and in those who previously had a vast, usually transmural myocardial infarction complicated by the formation of cardiac aneurysm. In other cases the protracted course of the disease is due to changes in the organism's reactivity under the influence of autosensitization by the products of disintegration of the heart muscle. The appearance of thromboendocarditis may also be conducive to transformation of the infarction into a disease with a characteristic relapsing course.

Protracted course of infarction is most commonly observed in elderly people with marked coronary atherosclerosis. Fever or periodically subfebrile rises in temperature sometimes last for months. In 20 of the 282 patients observed by Shestakov (1962) the febrile period persisted for more than 25 days. No complications that could have caused the protracted fever were found. Its uncommon persistence can be explained only by the processes developing in the heart itself.

The periodic rises in body temperature usually occurred after more or less intense pains in the heart region. The attacks of retrosternal pains in these patients are sometimes followed by a noticeable increase in the number of leucocytes in the blood. In a few days, sometimes in one or two, the number of leucocytes in the blood returns to normal in order to increase again after one of the angina pectoris attacks. The ESR remains accelerated over a period of seven or eight weeks. Sometimes it slows down or quickens. Simultaneously with an increase in the number of leucocytes the enzymatic activity and fibrinogen content of the blood serum increase in these patients in wavelike fashion.

The attacks of retrosternal pains are sometimes superseded by attacks of cardiac asthma, which develop particularly often in the third or fourth week of the infarction. Most commonly they occur at night. Sometimes a temporary enlargement of the liver or a transient appearance of puffiness of the shanks is observed. In some cases the aforesaid signs of heart failure soon disappear without leaving a trace, in others a clinical picture of chronic heart failure develops.

According to Bluzhas and Jankevichute (1965), Snow and others, the wavelike course of the disease is due to the formation of fresh necroses in the myocardium. The diversity of clinical manifestations above is due to the fact that foci of fresh necrosis form in the myocardium from the very beginning of the disease in addition to the reparation processes. The duration of the unstable equilibrium between the aforesaid processes depends on many factors the most important of which are apparently the patient's regimen and the extent of collateral circulation in the zones of the heart muscle adjacent to the necrosis.

Shestakov explains the protracted course of infarction by sharp

stenosing coronary atherosclerosis. Specifying this proposition Popov (1964) points out that under conditions of marked atherosclerosis the rate of organization and cicatrization of the infarction merely slows down. This could be accepted if, in addition to areas of maturing connective tissue, foci of fresh necrosis, dystrophy and necrobiosis were always observed in the infarction area.

Usually these microfocal or even fairly extensive necroses are located in the zone of maturing connective tissue or along its periphery. It is very difficult to diagnose fresh necroses on the posterior wall of the myocardium because, as a rule, they do not produce clear changes in the ECG. Other signs of circumscribed fresh necrosis are still less specific and their diagnostic significance can be correctly evaluated only in the aggregate.

Recurrent necroses in the anterior wall of the myocardium are diagnosed appreciably more easily. If they are located along the periphery of the primary infarction, they lead in most cases to characteristic changes in the ECG. In some cases the signs of primary infarction on the ECG become more distinct and are revealed in more leads than they were before the necrosis. In other, much more frequent cases, changes in the *STT* complex characteristic of subendocardial necroses appear in one or several leads of the ECG. Usually they are manifested by a depression of the *S-T* segment with a simultaneous inversion of the *T* wave. Sometimes the *S-T* segment elevates, its upward deflection becoming more convex than in the preceding ECGs, while the negative *T* wave becomes more pointed. An inversion of the negative *T* wave into a positive wave is sometimes observed.

When the location of the recurrent infarction does not coincide with that of the primary infarction, ECG in most cases shows signs of both. A partial levelling of the ECG signs of either the old or the new infarction is observed much less frequently. Sometimes the fresh infarction levels the ECG signs of the old infarction only for a short time.

Two or three weeks later signs of the old infarction that nearly disappeared reappear in the ECG. In multiple myocardial infarctions of various localizations the ECG may remain unchanged or reveal only the changes in the *RS-T* complex characteristic of affection of the subendocardial layer.

The aforesaid changes in the ECG arise simultaneously with more or less intense pains in the chest. The appearance of characteristic changes in the activity of blood enzymes and other signs of the resorptional necrotic syndrome combined even with transient disturbances in the cardiac rhythm or with attacks of cardiac asthma makes it possible confidently to associate the relapsing course of the disease with an appearance of fresh necroses in the myocardium.

Of special interest is the question of the frequency and periods of the appearance of fresh necroses in the myocardial infarction pa-

tient. We have observed a protracted course of infarction in connection with formation of fresh necroses in the myocardium in 5 per cent of patients.

Fresh necroses most commonly occurred at the end of the third and in the fourth weeks of the disease. According to Popov (1964), 31.7 per cent of new infarctions developed in the first two months of the disease.

Practical experience warrants the assumption that the diagnosis of fresh microfocal necroses appearing during convalescence from the preceding infarction must be based on signs of the resorptional-necrotic syndrome. The addition of more or less pronounced signs of acute left ventricular failure and disturbances in the cardiac rhythm indicate the appearance of rather extensive necroses which may appreciably alter the prognosis.

In summing up all the foregoing data it may be said that protracted course of infarction with recurrent left ventricular failure, arrhythmia and fever may be caused not only by such complications as the postinfarctional syndrome, thromboendocarditis and thromboembolism, but also by not simultaneous formation of necrosis. In these cases the entire disease may be conceived as a chain of myocardial necroses each of which appeared before complete recovery from the preceding one.

The term 'recurrent myocardial infarction' should be employed to designate the necroses of the heart muscle which develop only after complete recovery from the preceding disease. Recurrent infarction is therefore not an episode that complicates the course of the not as yet terminated disease, but is a new disease. Lukomsky and Tareev (1958) reported to the 14th Congress of Internists that recurrent infarctions are encountered in 17.7 per cent of cases.

Recurrent infarctions most commonly appear in the zone of the scars left by the preceding infarction and may be both extensive and microfocal.

The clinical picture of a recurrent infarction does not differ in principle from that of the primary infarction. The whole diversity of symptoms and signs of the recurrent infarction can be completely fitted into the aforesaid clinical syndromes. The pain syndrome dominated in the clinical picture of 80 per cent and acute heart failure was observed in 56 per cent of patients with an extensive recurrent myocardial infarction. The higher incidence of heart failure is due apparently to the older age of the patients with recurrent infarction; in it heart failure runs, as a rule, more severe course than in the primary infarction.

Recurrent microfocal infarction often assumes the character of cardiac asthma, a hypertensive crisis or disturbances in the cardiac rhythm, in which case the pain syndrome is not strongly pronounced and is sometimes absent. Modern diagnosis of infarction is mainly based on signs of the resorptional necrotic syndrome. But here, too, the physician often encounters considerable difficulties not only in

finding the signs, but also in interpreting the results. It is particularly difficult to evaluate the ECG changes.

Lukomsky has long since noted that in recurrent myocardial infarction the ECG changes do not fit into the types characteristic of primary infarction. In these cases the ECG picture forms as a result of integration of the signs of the old and the recurrent infarction. In some cases the signs of the old infarction are levelled out or, on the contrary, the ECG signs of the recurrent myocardial infarction are blocked, and the ECG shows only the changes caused by the earlier infarction.

Very helpful in the diagnosis of recurrent myocardial infarction are the results of dynamic determination of enzyme activity in the blood serum. It should be remembered, however, that the results of all laboratory tests may be normal and that sudden death may sometimes be the only indication of the recurrent myocardial infarction.

The prognosis of recurrent myocardial infarction is much graver than that of the primary infarction. The more frequent appearance of heart failure and other complications appreciably deteriorate the patients' chances of recovery and life.

6

DIFFERENTIAL DIAGNOSIS

Myocardial infarction is one of the diseases which have no constant clinical signs. Its external manifestations in various patients sharply differ from each other, thereby sometimes becoming the cause of diagnostic difficulties. The clinical picture in typical cases is so characteristic that a correct diagnosis may be made directly at the patient's bedside without using any laboratory methods. On the basis of personal experience we have collected the impression that typical cases of infarction have of late been less frequent than its atypical variants. Sometimes a correct diagnosis of the latter can be made only after more or less prolonged observation of the course of the disease, the dynamics of ECG changes and other laboratory tests.

The diagnostic errors arising in such cases may be divided into two categories. In some cases myocardial infarction remains unrecognized and diagnosis of some other disease is erroneously made. In other cases myocardial infarction is diagnosed where there is not any. The reason for it is that many internal and heart diseases begin with a clinical picture which largely resembles that of the incipient period of myocardial infarction.

In comparing admission and clinical diagnosis Shestakov (1962) found that myocardial infarction remains unrecognized in about half the patients sent for hospital treatment by physicians of various therapeutic institutions. Under conditions of polyclinic microfocal affections of the heart muscle particularly often remain unrecognized. Hyperdiagnosis of myocardial infarction is observed less frequently and usually does not lead to such tragic consequences.

In practical work it is most commonly necessary to make a differential diagnosis between myocardial infarction and angina pectoris without necroses in the heart muscle. The ability to distinguish these forms is of considerable practical importance. An established diagnosis determines the particular approach to the problems of treatment, regimen, periods of incapacity and sometimes the patient's occupation, for which reason every physician must be familiar with the principles of differential diagnosis of the various forms of coronary failure.

The clinical aspects and diagnosis of these forms of the coronary disease were studied in particular detail by Gefter (1951), Gvatua (1957), Shestakov (1962), Lukomsky (1964), Popov (1964) and Myasnikov (1965). In addition to myocardial infarction and uncomplicated angina pectoris (stenocardia) the foregoing authors distinguish the so-called transitional forms of coronary failure. According to Shestakov, among the transitional forms it is expedient to distinguish microfocal myocardial infarctions and angina pectoris complicated by 'affection of the myocardium'. By the term 'affection of the myocardium' Shestakov designates such affections of the heart muscle that have no morphological equivalent and are displayed only by the disturbances in certain functions of the myocardium such as excitation, conduction of the electric impulses and permeability of cell membranes.

Myasnikov divided transitional forms of coronary failure into angina pectoris with microfocal necroses of the myocardium and focal dystrophy of the heart muscle. By the term 'focal dystrophy' he designated changes in the myocardium that have not reached the stage of necrosis. The classifications differ from each other in fact only in terminology, and so in practical work they can be used as equivalents. It is merely desirable that the diagnosis should indicate the cause of the focal injury or the focal dystrophy of the myocardium.

It is considered that attacks of pain in uncomplicated angina pectoris usually arise under a physical load or at rest, last about five or ten minutes and in most cases are easily eliminated by nitroglyceryn (glyceryl trinitrate or trinitrin) or Validol (menthyl valerate). During attacks of pain and directly after them the body temperature remains normal, and the leucocyte count and leucocyte formula of the blood are unchanged. Uncomplicated angina pectoris even during frequent attacks is not accompanied with changes in the form of the individual elements of the ECG.

During attacks of coronary failure microfocal dystrophy of the myocardium is attended with changes in some functions of the heart muscle; most commonly they are revealed during electrocardiography. In some patients with coronary atherosclerosis attacks of angina of effort are always accompanied with extrasystoles, the unchanged form of which indicate that they come from the same portion of the left ventricle. In other, more frequent cases the ECGs recorded during or imme-

diately after the attack of angina pectoris show depression of the *S-T* interval. In these cases the *T* wave either is not changed, or flattened or changed from positive to negative. Isolated changes in the *T* wave (as its inversion or flattening) and an upward displacement of the *S-T* interval with a simultaneous change of the *T* wave into a negative wave occur less frequently. Novikov and Kuzmina (1963) observed in these patients a temporary bundle-branch block.

The foregoing changes in the ECG arise as a result of focal injuries to the myocardium. Of themselves they indicate only the existence either of foci of dystrophy or necroses in the subendocardial regions of the heart muscle. The connection between these changes and the state of coronary circulation is established on the basis of the results of clinical examination and observation of the patient.

In focal myocardial dystrophy the activity of blood transaminases does not usually change and the temperature remains normal. The blood leucocyte count is unaltered, the leucocyte formula is also unchanged and the ESR is not accelerated.

The pain syndrome is usually more strongly pronounced than in uncomplicated angina pectoris. The pains arise not only under physical loads but also at rest. Their duration may vary within rather wide limits. In evaluating this symptom it is necessary to remember that the attacks of retrosternal pain of several minutes' duration do not exclude the possibility of necroses in the heart muscle, while in attacks lasting more than 10-15 minutes the appearance of necroses in the myocardium is very probable.

The assumption of the presence in the myocardium of fresh foci of necrosis becomes still more convincing, if the attacks of pain are attended with a moderate increase in the leucocyte count, which Shestakov designated by the term 'leukocytic candles'. The leucocyte formula changes negligibly. Sometimes a shift to the left is noted; the ESR is occasionally accelerated. The temperature in microfocal necroses of the myocardium may remain normal, but at times it rises to subfebrile figures in the course of one or two days.

The diagnostic significance of the changes in the activity of serum enzymes has of late been intensively studied. Some authors are even inclined to regard almost any increase in the activity of aspartic aminotranspherase (glutamic-oxal-acetic transaminage) in a coronary atherosclerosis as a quite convincing criterion of myocardial necrosis. It was already noted above that myocardial infarction is almost always accompanied with an increased activity of the serum enzymes, especially that of aspartic aminotranspherase. From this it does not follow, however, that any increased activity of aspartic aminotranspherase or other enzymes in the serum justifies the diagnosis of microfocal necroses or even myocardial infarctions. In evaluating the results of the laboratory tests it is necessary to remember that myocardial infarction is only one of the many causes of increased activity of these blood serum enzymes.

The final diagnosis must be based on clinical observation of the course of the disease, the dynamics of changes in body temperature, the ESR and the composition of the formed blood elements. Special importance must be attached to the ECG changes.

Subendocardial necroses of the myocardium are displayed in the ECG by a lowering of the *S-T* interval which is attended with the change in the *T* wave described above. Most commonly these changes appear in leads V_4, V_5 and standard lead II. The inversion of the *T* wave or its levelling in these or other leads in focal necroses persists for one or two days and sometimes longer.

It is clear that to reveal this sign it is vital to repeat, desirably daily, the electrocardiographic study of the patient. The diagnostic significance of the foregoing ECG changes sharply increases if they appear in the patient immediately after the attack of retrosternal pains and do not disappear after their cessation.

It is particularly difficult to reveal the focus of necrosis in the posterior wall of the left ventricle in patients with bundle-branch block. A correct interpretation of the ECGs in these cases is possible only after a detailed study of the clinical course of the disease. The appearance of even transient arrhythmias, or the development of, or increase in, signs of heart failure indicate focal myocardial necroses even in cases where the leucocyte count and the body temperature remain normal.

Acute coronary failure with microfocal necroses of the myocardium occurs particularly often in patients who have already survived a vast myocardial infarction. The clinical manifestations of coronary failure in these patients may be extremely atypical, which considerably complicates the diagnosis. A patient with extensive cicatricial changes in the myocardium after surviving an infarction often does not complain either of pains in the chest or dyspnoea, and the physician sometimes does not even suspect that the sweating and weakness which appeared seemingly without any reason conceal coronary failure with microfocal necroses.

These patients sometimes develop cardiac asthma or left ventricular failure. Atrial flutter occasionally appears and then cardiac asthma is often erroneously associated with the tachycardiac form of cardiac arrhythmia and not with the underlying microfocal miocardial necroses. In some cases the character of angina pectoris sharply changes. Validol (menthyl valerate) and nitroglycerin, which have helped the patient in the course of many years, suddenly cease to produce an analgetic effect.

Clinical signs of themselves do not warrant a diagnosis of microfocal infarction, but combined with the aforesaid ECG and other laboratory signs their diagnostic value is appreciably altered. Careful clinical examination of all the data obtained as a result of recurrent examinations of the patient makes it possible to establish correct diagnosis in the overwhelming majority of cases.

It is sometimes necessary to distinguish myocardial infarction

from acute benign pericarditis in which, like in myocardial infarction, pain in the chest is at times attended with a fever and pericardial friction murmur. The diagnosis is considerably facilitated, if some peculiarities of the combination of the pain syndrome with fever and the ECG results are taken into account.

In pericarditis pains in the chest may have exactly the same localization as in some forms of myocardial infarction. They are seldom intensive, but no diagnostic importance should be attached to this sign because pains in myocardial infarction may be not only severe, but also barely perceptible.

Of some diagnostic significance is the connection between the pain and movements. In myocardial infarction the pains do not depend on the patient's position in bed, whereas in pericarditis they definitely increase during movements, turns of the body and changes in position in bed. They often become noticeably milder when the patient changes from a lying to a sitting position.

In myocardial infarction the pain syndrome precedes fever and ESR acceleration, whereas in acute pericarditis it appears simultaneously with fever and ESR acceleration. The pericardial friction murmur in myocardial infarction may be transient and delicate. In pericarditis it is always clearly auscultated and usually persists over a period of one or two weeks. Exactly the same murmur occurs in the postinfarctional syndrome and auscultation of the friction murmur, therefore, makes it possible to diagnose pericarditis, but rarely helps to solve the problem of its aetiology.

The ECG changes in infarction and in acute pericarditis are not always easy to distinguish from each other because they arise in both cases as a result of affection of the heart muscle. In studying the ECG it is necessary to pay special attention to the following signs:

1. A deep and wide Q_1 or Q_3 wave combined with characteristic changes in the STT segment is a typical sign of anterior or posterior myocardial infarction. In pericarditis the Q wave is either not pronounced or only barely outlined in the standard leads.

2. During the incipient period of pericarditis the S-T segment is convex and, what is particularly characteristic, usually elevated in all three leads, whereas in myocardial infarction the S-T segment in leads I and III always deviates in opposite directions.

3. In pericarditis the R wave in chest leads nearly always persists, only its amplitude decreases, whereas in myocardial infarction the QRS complex may become deformed to such an extent that the R wave sometimes completely disappears.

4. S-T segment elevation in the standard leads sometimes occurs in myocardial infarction complicated by pericarditis. But in these cases the subsequent ECGs show deep Q_1 and Q_3 waves and formation of typical negative T_1 and T_3 waves.

In later stages the diagnosis of pericarditis may be confirmed by X-ray. The changes in the dimensions and form of the heart may

be revealed in a series of radiographs. The method of radio-isotope scanning of the heart and liver with the use of human serum albumin and colloid gold, which was suggested in recent years, also appreciably facilitates the finding of exudate in the pericardial cavity.

In dissecting aneurysm of the aorta the pain syndrome almost always occurs on a background of a clinical picture which is difficult to distinguish from that of myocardial infarction. Intense pains in the chest in cases of dissecting aneurysm are often attended with syncope, profuse sweating, tachycardia and dyspnoea. Several hours later the pains subside and resemble the appearance of spacies lucidum which occurs in myocardial infarction. The subsequent development of heart failure increases the resemblance of dissecting aneurysm to myocardial infarction still more.

The basis of differential diagnosis between myocardial infarction and dissecting aneurysm may be primarily the data obtained by questioning the patient about the peculiarities of the appearance and course of the pain syndrome. In dissecting aneurysm pain always arises suddenly, whereas in myocardial infarction it is often possible by patiently questioning the patient to reveal the so-called pre-infarctional period during which the pain was gradually intensified.

As was already noted, in myocardial infarction the pain sharply increases and reaches maximum intensity about half an hour after the onset of the disease. In dissecting aneurysm it is the most intense in the very beginning of the disease, i.e. at the moment of aortic rupture. If the patient survives this moment, in the days and sometimes even hours that follow the pain sensations gradually abate and may disappear almost completely until the point of death which usually occurs suddenly.

Pain in dissecting aneurysm differs from this in myocardial infarction not so much by its localization and irradiation, as by the ability to migrate. Starting in the region of the scapulae, behind the sternum or in the upper part of the abdomen the pain in dissecting aneurysm begins to be felt several hours later in the shoulders, small of the back, the region of the thighs, inguinal region and the lower extremities. In myocardial infarction this succession of the spread of pain is not observed.

Of considerable diagnostic significance are also the results of repeated measurement of arterial pressure. Despite the intense pain which is not eliminated even by morphine the arterial pressure in a patient with dissecting aneurysm usually persists at the normal level. In the cases we observed it was even elevated. The pain syndrome of an equal or even lesser intensity in a myocardial infarction patient is usually a precursor of the developing shock. Persistence of arterial pressure at the normal level or even hypertension in the incipient stages of the disease is an important symptom which in most cases helps to distinguish dissecting aneurysm from myocardial infarction.

Dissecting aneurysm most commonly appears in persons affected with hypertension, for which reason the ECGs recorded in the beginning of the disease very often show signs of left ventricular hypertrophy. Sometimes the ECG shows signs of ischaemia of the subendocardial layers of the myocardium in the form of a lowered *S-T* segment with concomitant changes in the *T* wave. Sometimes, old cicatricial changes in the myocardium are found. Typical ECG signs of fresh infarction are not observed. Negative results of the repeated electrocardiography warrant reliable exclusion of possible myocardial infarction.

In most cases aortic rupture occurs in places further away from the site where the subclavian artery branches from it. In rupture of the intima over the aortic valves signs of occlusion of the aortic arch and the coronary arteries may appear. Depending on the extent of the process the patient may exhibit disorders in vision, hemiplegia (the results of occlusion of arteries branching from the aortic arch), paraplegia and other neurologic disturbances (resulting from ischaemia of the spinal cord), ileus and intestinal infarction (occlusion of the celiac artery) and disturbances in the function of the pelvic organs. The successive development of these signs sometimes enables one to suspect dissecting aneurysm.

In dissecting aneurysm, like in myocardial infarction, death usually occurs suddenly or very soon. According to McCloy *et al.* (1965), more than half the patients die during the first weeks and 63 per cent during the first two weeks of the disease. Very few of the patients live for more than one year. In most cases death is caused by rupture of the dissecting aneurysm into the pericardial or pleural cavities or other organs.

Although dissecting aneurysm differs from myocardial infarction in its clinical manifestations and course, it is often not recognized intravitally, possibly because of the physicians' insufficient knowledge of this disease. Meanwhile this error in diagnosis may lead to serious consequences because in dissecting aneurysm treatment with anticoagulants is contra-indicated.

Pulmonary thromboembolism is a frequent complication of myocardial infarction and one of the main causes of an unfavourable outcome of the disease. The clinical picture of pulmonary thromboembolism is very diverse. Occlusion of the main trunk of the pulmonary artery always ends in the patient's sudden death. Occlusion of the smallest branches of the pulmonary artery is often not recognized intravitally because it has no characteristic symptoms.

Occlusion of large branches of the pulmonary artery leads to the development of the clinical picture of acute pulmonary heart, collapse, pulmonary infarction, syncope, attacks of tachycardiac arrhythmia, asthma and pulmonary oedema. According to certain authors, pulmonary thromboembolism is attended with pains in the chest in 35 per cent of cases, which may sometimes be localized behind the sternum thereby simulating coronary failure (Teodori,

1956). In pulmonary infarction the pains are like those in myocardial infarction; sometimes they irradiate into the hypochondrium and may become the cause of erroneous diagnosis of a disease of the abdominal organs.

The aforesaid syndromes are often also observed in the acute period of myocardial infarction. In such cases the patient's fate largely depends on the physician's ability correctly to evaluate the cause of the appearance of the syndromes.

In making a differential diagnosis between myocardial infarction and pulmonary thromboembolism it is necessary first of all to study the anamnesis. Although an acute onset is characteristic of both diseases, the myocardial infarction patient remains, as a rule, physically active until the very onset of the disease, whereas pulmonary thromboembolism usually occurs in a patient who before the onset of the disease was more or less bed-ridden in connection with an operation, chronic circulatory insufficiency, exacerbation of thrombophlebitis or parturition.

Attacks of angina pectoris often precede myocardial infarction. This symptom becomes significant for differential diagnosis only when angina pectoris appeared or sharply increased shortly before the suspected infarction. Its significance appreciably decreases in patients with recurrent infarctions, suffering from chronic angina pectoris over a more or less long period of time. In differential diagnosis between myocardial infarction and pulmonary infarction special importance is attached to the appearance of signs of acute or subacute pulmonary heart and the peculiarities of the clinical course of the disease.

Occlusion of the main branches of the pulmonary artery is often complicated by collapse the characteristic signs of which are an increased venous pressure and the so-called pale cyanosis of the skin and mucosa. The fear of death is observed as often as in myocardial infarction. In these patients hypotension develops as a result of an acute fall of the minute volume, as well as the active unloading reflexes appearing during a rise in arterial pressure in the pulmonary artery (Parin, 1960).

Thus, whereas the development of acute left ventricular failure is characteristic of myocardial infarction, pulmonary thromboembolism is characterized by the development of acute right ventricular failure, and in less severe cases by an acute or subacute pulmonary heart, the clinical picture of which is composed of symptoms appearing in connection with acute overstrain and dilatation of the right ventricle.

Pulsation in the second and third intercostal spaces left of the sternum, swelling of the cervical veins, the appearance of systolic murmur, accent and doubling of the second sound on the pulmonary artery do not occur in every case of acute and subacute pulmonary heart and therefore cannot be regarded as in any way reliable signs for the differential diagnosis.

The classical signs of pulmonary infarction (haemoptysis, fever and pains in the chest) are revealed in not more than half the cases of pulmonary thromboembolism. Moreover, two of these three main signs may also occur in myocardial infarction. Leucocytosis, accelerated ESR, increased activity of transaminases about equally often take place both in myocardial and pulmonary infarction. The differential diagnosis between myocardial infarction and acute pulmonary heart is based mainly on the result of ECG and X-ray methods of study.

Lepskaya (1963) points out the considerable diagnostic significance of the radiographic signs of occlusion of the main trunks of the pulmonary artery: the root 'amputation' symptom with its dilatation proximal to the site of thrombosis and Westermark's symptom displayed by an increased transparence of pulmonary tissue in the zone of branching of the thrombosed arterial branch, bulging of the cone and arch of the pulmonary artery and enlarged right ventricle. In the presence of portable X-ray apparatus the foregoing symptoms can be revealed on the first day of the disease.

The ECG results are of particular significance for differential diagnosis. The development of acute pulmonary heart is accompanied with a clockwise turn of its axis with a shift of the anterior zone to the left. As a result an intermediate or vertical electric position of the heart is revealed in the acute stage in most patients. In a detailed study of 135 autopsy cases of pulmonary thromboembolism in the first day Zlochevsky (1965) found the ECG signs of acute pulmonary heart in 77 per cent of cases. Other authors report about the same findings.

The diagnosis of acute pulmonary heart may be made on the appearance of deep S_1 and Q_3 waves (S_1-Q_3 syndrome), a negative T_3 wave and an increased R_3 wave. The T_2 wave may be diphasic or negative.

The following characteristic changes take place in the chest leads: the T wave becomes negative in leads $V_{1,2,3}$ and sometimes in lead V_4, the transitional zone shifts to the left to lead V_4 or even V_5. The T wave in the right chest leads, usual ($V_{1,2}$) and distal (V_{6R}—V_{3R}), becomes negative. There is a displacement of the S-T segment upward in leads III, a VF and a VR and downward in leads I, II and VI. Sometimes P pulmonale, paroxysm of cardiac arrhythmia and attacks of paroxysmal tachycardia appear.

Negative T waves in leads II, III, a VF and in the right chest leads begin to form two or three days later. The dynamics of the changes in Q_3 and T_3 are similar to those in myocardial infarction of the posterior (diaphragmatic) wall of the left ventricle. The negative waves become deeper and more symmetrical, and one or two weeks later a reverse development of these changes begins.

Many authors explain the foregoing changes in the QRS complex in pulmonary thromboembolism either by the appearance of myocardial ischaemia or the development of microfocal necroses in the posterior wall of the left ventricle during collapse.

Zuckermann (1966) points out the following signs which help to distinguish acute pulmonary heart from infarction of the posterior wall of the left ventricle:

(1) in acute pulmonary heart the Q_3 wave is deep but not wide (less than 0.04 sec), while the Q_2 wave is usually not pronounced;

(2) rapid and complete normalization of the ECG;

(3) lowering of the S-T_2 segment, whereas in myocardial infarction it is elevated.

Zlochevsky (1965) discovered the following additional differential-diagnostic signs:

(1) the deepening of the Q_3 wave in acute pulmonary heart is attended with an increase in the R_3 wave;

(2) absence of stable changes in the left chest leads V_5 and V_6, which in myocardial infarction often indicate affection of the lateral wall of the left ventricle.

Pulmonary thromboembolism in a patient with a fresh myocardial infarction and in a patient with cicatricial changes in the heart muscle leads to the appearance in the ECG of the foregoing signs of the clockwise turn about the long and anteroposterior axes of the heart. Special importance is attached to the increase in the R_3 wave with preservation of the pathological Q_3 wave, the appearance of high and wide $P_{2,3}$ waves and splitting of the QRS complex in the right chest leads, in leads $V_{1,2}$ and $V_{6R\text{-}3R}$, and lowering of the formerly elevated S-T_2 interval.

Signs of acute and subacute pulmonary heart usually appear in occlusion of the main or lobar and sublobar branches of the pulmonary artery. Occlusion of smaller branches of the pulmonary artery may not be followed by pulmonary infarction. The clinical signs of embolism in these cases usually amount to the appearance of the seemingly causeless tachycardia and fever that does not yield to antibiotics. The inexplicable dyspnoea, syncopes, acute falls of arterial pressure and development or aggravation of heart failure are sometimes the only signs of embolization of the pulmonary artery.

When the foregoing symptoms develop in the subacute stage of myocardial infarction only long observation of the course of the disease makes it possible to distinguish the clinical picture of embolization of small branches of pulmonary artery from the clinical picture of recurrent necroses of the heart muscle or the postinfarctional syndrome[1]).

Myocardial infarction often has to be differentiated from acute diseases of the digestive organs. In some cases the diagnostic difficulties arise as a result of pain localization in the epigastric region or in the abdomen, in others as a result of complete or almost complete absence of pains.

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[1]) See also Chapter 5, Part 2.

Strongly pronounced pains are sometimes attended with nausea and vomiting. If they are localized in the right hypochondrium, they may be erroneously regarded as acute cholecystitis or (as was the case described by S. P. Botkin) an attack of hepatic colic. This assumption becomes still more probable, if the patient had attacks of hepatic colic before.

In many such cases a detailed anamnesis helps to make a correct diagnosis. In hepatic colic the pain reaches its culmination in the course of a few minutes, whereas in most cases of myocardial infarction the pain increases in wavelike fashion and becomes the most intense about half an hour or one hour after its appearance. Hepatic colic is nearly always accompanied with nausea due to the increased pressure in the bile ducts. Nausea is also observed in the acute period of myocardial infarction, especially after administration of morphine. The absense of nausea at the height of the pain syndrome is an indirect sign of myocardial infarction.

Palpation of the right hypochondrium is also of some diagnostic significance. In the beginning of the pain attack the sensitivity in the region of the gall bladder may be absent in both diseases. Several hours later symptoms indicating inflammation of the gall bladder usually appear in the patient with hepatic colic. Palpation in the region of the gall bladder becomes even painful. The pain often increases with deep inhalation. In cholelithiasis and acute cholecystitis the liver may be painful usually only in the region of the gall bladder, whereas in myocardial infarction, owing to acute swelling, both the right and left lobes of the liver are painful.

Myocardial infarction is often attended with general weakness and a sense of exhaustion, which appear in the beginning of the disease in combination with sweating. In the incipient period of the pain attack in cholelithiasis there is neither weakness nor any feeling of exhaustion. Pain and not weakness prevails in the clinical picture. It may be considered even intravitally that the severity of the condition in acute cholecystitis corresponds to the intensity of the inflammatory phenomena in the region of the gall bladder, i.e. the intensity of pains, the extent of muscular defence, fever and leucocytosis. On the other hand, the myocardial infarction patient usually produces a graver impression despite the absence of signs of muscular defence.

Of invaluable significance are also the data on the peculiarities of the pain irradiation. A repeated examination sometimes half an hour or an hour later often reveals that in addition to the pains in the hypochondrium, the myocardial infarction patient developed pains in the chest, neck, shoulders or the left arm. The force of the first heart sound sometimes changes, the cardiac rhythm is disturbed or the arterial pressure sharply falls in this period.

The clinical evaluation of the foregoing symptoms and signs depends largely on the anamnesis which must be collected in these cases particularly carefully. In all cases, wherever possible, it is

necessary to record an ECG which often enables the physician to establish a diagnosis.

If the abdominal pains are combined with a fall of arterial pressure, the myocardial infarction patient often develops a picture of shock which may be erroneously diagnosed as a consequence of acute abdomen that arose during perforation of gastric ulcer or as collapse in acute pancreatitis. Errors of this kind are rare, but they nevertheless take place. They may be avoided only by careful evaluation of the anamnesis and objective examination.

In myocardial infarction the abdomen is often inflated, whereas perforation of an ulcer is characterized by a sunken abdomen. In myocardial infarction patients the tension of the abdominal wall is usually not constant. By distracting the patient's attention it is usually possible to note that it decreases or even disappears completely. The distraction of the patient who has a perforated ulcer does not affect the extent of muscular defence.

The appearance of retrosternal pains or the spread of pains to the thorax and upper extremities, as also tachycardia during the incipient period of the disease or typical ECG changes are evidence of myocardial infarction. The disappearance of hepatic dullness and appearance of free air in the abdominal cavity warrant the diagnosis of perforated ulcer.

It is much more difficult to distinguish myocardial infarction from acute pancreatitis owing to the similarity between the main clinical manifestations of both diseases, as well as the possibility of their simultaneous appearance in the same patient.

The problems of differential diagnosis between pancreatitis and myocardial infarction deserve the closest attention because the therapeutic measures which often save the pancreatitis patients are fatally dangerous to the myocardial infarction patients.

Both diseases often begin with acute, tormenting pains to which may be added a clinical picture of collapse or shock. The addition of a frequent similarity between the laboratory signs of both diseases makes it apparent that the differential diagnosis between them is in most cases an art based on an ability to evaluate mainly the shades of the very same signs and symptoms. The fear of death and general anxiety are frequent signs of acute pancreatitis (Shelagurov). As was pointed out above, these symptoms are also typical of myocardial infarction.

Pain in the upper part of the abdomen with irradiation to the left arm, left shoulder, left scapula or the interscapular region is considered characteristic of acute pancreatitis. The same localization of pains occurs in about 5-6 per cent of myocardial infarction patients. According to summary data of Lashchevker (1969), the most intense pains in pancreatitis are localized in the retrosternal region in 5 per cent of cases. Left-sided irradiation of these pains may completely coincide with their irradiation in myocardial infarction. It should be noted, however, that in pancreatitis the pain begins

acutely and is constant. Myocardial infarction is characterized by a wave-like intensification of pain.

Painfulness in the epigastric region in both diseases is not accompanied with the appearance of marked rigidity in the anterior abdominal wall. Pancreatitis usually involves phenomena of gastric and intestinal paresis, more or less intense meteorism and recurrent bilious vomiting. Pancreatitis is characterized by protracted pains in the epigastric region. In uncomplicated myocardial infarction the pains usually persist only a few hours. Marked meteorism and recurring vomiting in a myocardial infarction patient must always impel the physician to think of concurrent pancreatitis.

The ECG method of examination is very helpful in diagnosing myocardial infarction, but on suspicion of pancreatitis the data obtained must be very carefully evaluated. Acute necrosis of the pancreas is usually attended with a clinical picture of collapse or shock. A sharp fall of arterial pressure and, consequently, of perfusional pressure in the coronary arteries may become one of the causes of the development of coronary failure the ECG signs of which (lowering of the *S-T* segment and the appearance of a negative or diphasic *T* wave in one or even several leads) are observed in about half the patients with acute pancreatitis. The ECG signs of coronary failure in cases of serous pancreatitis last a comparatively short time, but in necroses of the pancreas they may persist for several weeks.

Pancreatitis sometimes involves disturbances in intraventricular and atrioventricular conduction and the appearance of extrasystoles and even cardiac arrhythmia. Petrov and Lobachev (1956), Bockus (1966), and others report cases of acute pancreatitis with ECG changes typical of myocardial infarction.

The disturbances in rhythm and conduction, and the foregoing ECG changes in pancreatitis probably appear as a result of focal necroses which develop in the myocardium under the influence of the proteolytic enzymes that enter the blood from the pancreas in cases of its necrosis (Elkonkin and Shimelinovich, 1964). Under the influence of proteolytic enzymes acute pericarditis sometimes develops in pancreatitis patients, which causes pains in the cardiac region and probably disturbances in the cardiac rhythm.

The importance of the resorption-necrotic syndrome for differential diagnosis is also very limited. Necrosis of the pancreas usually involves high leucocytosis and absolute lymphopaenia. The activity of the blood transaminases increases in both diseases, but in extensive infarction to a much greater extent than in pancreatitis.

The studies of the activity of pancreatic enzymes are unfortunately also of little help to differential diagnosis between acute pancreatitis and myocardial infarction. The activity of blood amylase and urinary diastases increases not only in pancreatitis, but also in pneumonia, perforated gastric ulcer and other acute diseases of the abdominal organs. The activity of these enzymes noticeably increases

under the influence of morphine, pantopon and other drugs constantly used in the treatment of myocardial infarction.

According to clinical findings, urinary diastase of more than 512 units definitely indicates the presence of an independent or concurrent acute pancreatitis in a myocardial infarction patient. It should be noted that normal activity of diastase does not exclude the diagnosis of acute haemorrhagic pancreatitis (Moiseev and Filimonova, 1969).

Observation of the course of the disease and repeated examination of the patient with repeated determination of the aforesaid tests may appreciably facilitate the differential diagnosis between myocardial infarction and acute pancreatitis. Unfortunately this is not possible in all cases, and differential diagnosis between myocardial infarction and acute pancreatitis continues to be one of the most urgent problems.

In the incipient period of myocardial infarction and acute pancreatitis diarrhoea is sometimes added to the nausea and vomiting, which appears probably as a result of a vasovagal (viscero-visceral) reflex. This is usually observed in elderly people and is often accompanied with collapse. Sometimes the diagnosis of food poisoning is erroneously made in these cases.

To avoid diagnostic errors in all such cases, it is always necessary in collecting the anamnesis to question the patient in detail concerning pains in the region of the thorax. Lukomsky holds that on the appearance of unmotivated collapse, especially in elderly people, it is always necessary to think of possible myocardial infarction and to record an electrocardiogram without fail.

7

ELECTROCARDIOGRAPHIC CHANGES

In clinical electrocardiography myocardial infarction is considered one of the so-called focal affections which usually include: (1) acute myocardial infarction with its variants (protracted, relapsing, etc.); (2) local scars and (3) cardiac aneurysm.

The ECG curve indicating focal changes has certain morphological characteristics which have not caused any particular diagnostic difficulties since it was described by Pardee (1920, 1925).

At the same time the correlation between the ECG changes and the pathophysiological basis of the process, its morphological essence, localization of the lesion and certain other problems have until recently served as a subject of study.

The results of experimental, pathoanatomical and special electrophysiological studies determine a number of propositions of clinical electrocardiography in the interpretation of focal affections of the heart muscle. First, it is recognized that ECG diagnosis of focal affection is based primarily on the possibility of obtaining information on the remoteness of the developing process, i.e. on the possibility of differentiating, in the group of focal affections, between acute myocardial infarction and cicatricial changes and aneurysms on the basis of the dynamics or stability of the characteristic signs. Second, the ECG shows the zonality in the structure of the pathological focus or indicates the existence of three intertransitional zones: necrosis, lesion and ischaemia. Third, the ECG makes it possible to evaluate the various layers of the heart muscle involved in the process, from subendocardial to subepicardial. Fourth, on the ECG basis it is possible to establish the localization of the affection of the various regions or 'walls' of the heart.

The main morphological characteristic of the ECG changes due

to focal affection of the myocardium is the so-called monophasic curve. It is the four aforesaid approaches to consideration of the changes in the character of the monophasic curve that determine the specified diagnosis of focal affection.

In most cases acute myocardial infarction is well diagnosed clinically. The picture of chronic coronary failure in a cicatricial lesion of the heart muscle, as also the clinical symptoms of cardiac aneurysm, makes it possible to differentiate them from acute myocardial infarction without considerable difficulties. But in differential diagnosis between myocardial infarction and other noncoronarogenic processes in the heart accompanied with cardialgia, or between myocardial infarction and other, e.g. inflammatory, process of some other thoracic organ, the ECG data often prove to be decisive. A number of functional disorders, especially those accompanied with arrhythmia, undoubtedly require ECG analysis to exclude myocardial infarction. It may be said with confidence that precisely in myocardial infarction the role of electrocardiography for differential diagnosis is very important, although, naturally, not absolute.

Electrocardiographic Diagnosis of Focal Affections of the Myocardium

Modern ECG diagnosis of focal affections of the myocardium is based on the idea that in the affected part of the heart muscle the processes of depolarization and repolarization are completely distorted, which affects the general character of the potentials of the entire electrical field of the heart. This is manifested in monophasic ECG curves not only in the precordial leads, but also in the most remote parts of the body (leads from the limbs).

Unlike a normal diphasic ECG curve on which two phases of the electric process are clearly differentiated—the depolarization phase (the first positive deflection in the form of the *QRS* complex) and the repolarization phase (the second positive deflection in the form of the *T* wave), on a monophasic curve of the classical type it is impossible clearly to demarcate the successive change in the phases of the electric process; represented by one negative deflection the initial complex of ventricular activation (the *QS* wave) without a distinct border passes into an arched curve of the so-called current of injury which absorbs the *T* wave or 'overlaps' the repolarization phase. That is why only the total duration of the entire ventricular *QRST* complex and its morphological peculiarities are determinable in time on the monophasic curve, whereas the duration of the polarization phase can be evaluated only approximately, estimation of the temporal relations between both phases (depolarization and repolarization) being generally impossible.

In clinical electrocardiography, however, it is not always possible to find a typical monophasic curve as the chief criterion of

the acute focal affection. This depends both on the time of registration and the relation of the localization of the focus in the heart to the position of the electrodes and the direction of the axes of the chosen leads.

The later the periods from the onset of the infarction and the further away from the pathological focus the leads of the recorded

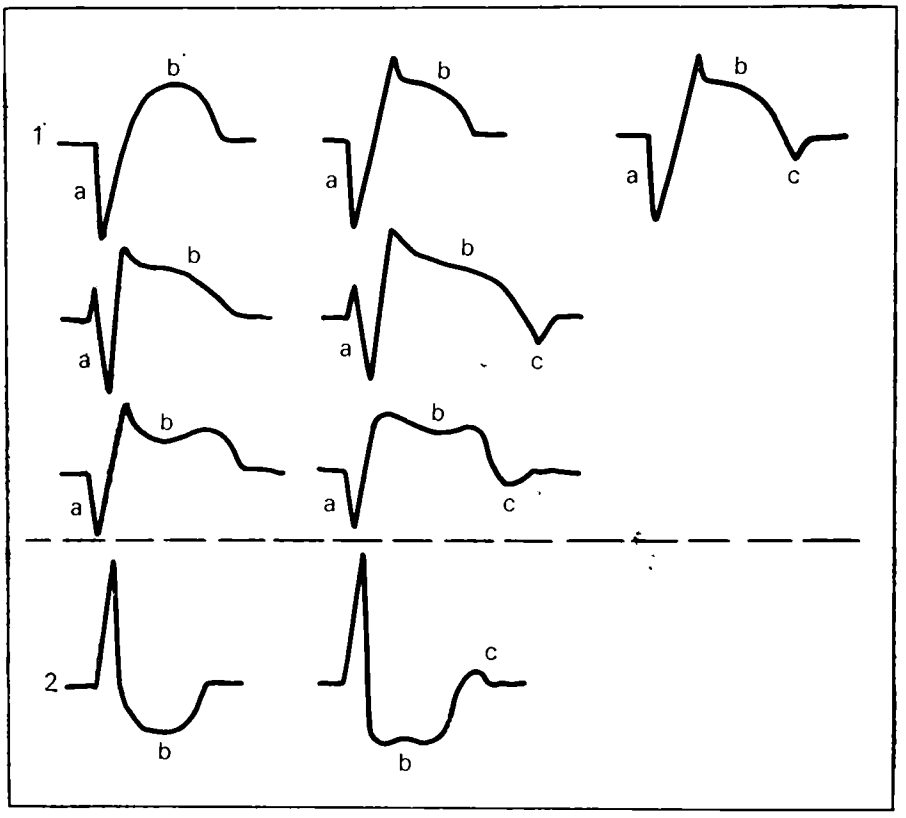

Fig. 56. Most common variants of the monophase ECG

1—morphology of monophasic curve in transmural, subepicardial and intramural focal heart affection; *2*—morphology of the monophase curve in subendocardial focal heart affection; *a*—prevalence of negative deflection in the *QRS* complex in the first phase of the process of cardiac excitation (during the depolarization period); *b*—current of injury completely or partly merging with the *T* wave or absorbing the second phase of cardiac excitation (superimposed on the repolarization period); *c*—residual deflection of the second phase of the ECG curve

curve, the more effaced the signs of monophaseness. As a matter of fact, in focal changes the classic monophasic curve is found only as one of the many translational variants of curves from different leads (Fig. 56). Many variants of the monophasic curve have in the initial part of the ventricular complex a late reduced *r* wave, in which case it is possible with considerable precision to judge of the duration of depolarization or at least of the time of ventricular activation by the *Qr* complex. Certain curves reveal in their terminal part some phases of the distorted or residual repolarization incompletely absorbed by the current of injury curve (see Fig. 56*c*).

In a normally functioning heart the electric potential of the depolarization period is recorded intracardially as a single negative complex (*QS* or rSr^1 complex) and on the external surface of the heart as a single positive complex (*qRs* or *R* complex). Curves may be recorded at various levels of the myocardium with the transitional configuration of the *QRS* complex (successively *Qr*, *QR*, *qR* complexes) from its negative (*QS*) to positive (*R*) value. In connection with this it is considered that the normal passage of the wave of excitation in the depolarization period in the direction from the subendocardial to the subpericardial layers of the heart is attended with a gradual transformation of the negative intracavitary potential into a positive potential of the external myocardial layer.

In focal affection the initial deflection of the monophasic curve recorded in the leads from the surface of the body as a negative *QS* (or *QR*) wave has mainly two interpretations in clinical electrocardiography based on experimental findings. The first conception formulated by Wilson *et al.* (1933) explains the appearance of the initial negative deflection on the ECG by direct transmission of the negative intracavitary potential to the surface through the electrically inert layer of the necrotized myocardium as through an open window. In this case the following variants are possible:

1. If the portion of electrically unexcitable dead tissue embraces the whole thickness of the myocardium, the tissue manifests itself as a passive conductor and does not modify the negative intracavitary potential which is transmitted to the surface in the form of a *QS* wave. The subsequent cicatrization of the transmural focus retains the property of electric inexcitability, and the *QS* complex persists on the ECG recorded from the surface as a constant sign of a focus of destruction in the myocardium.

2. The *QR* complex appears either in a case of direct transmission of the intracavitary potential through the affected region of the subendocardial layer and active formation of the positive potential in the form of a late *R* wave in the intact subepicardial layer, or on condition that living muscle fibres in the centre of the transmural scar are preserved.

The second conception arose as Prinzmetal's well-known revision of Wilson's conception.

According to experiments of Prinzmetal the internal layers of the myocardium normally manifest their electric properties by producing the *QR* complex similar to the intracavitary negative potential. This zone of normal reproduction of the negative *QS* complex in the internal layers constitutes about 80 per cent of the total thickness of the heart muscle. It follows that the positive *QRS* complex normally recorded from the surface of the heart reflects the character of depolarization of only relatively thin superficial layer of muscle of the free wall of the left ventricle, and of the central part and the right wall of the interventricular septum.

Two types of correlation were found on comparison of the electro-

grams recorded from the surface of transmural infarction with histological data.

One type of *QS* was recorded during complete absence of viable tissue in the underlying myocardium. This indicated that the negative superficial potential was conducted directly from the cavity not undergoing any changes.

The second type of the *QS* complex was found over the foci of affection containing islets of living tissue of muscle fibres which, at least partly, must have taken part in forming the potential recorded on the surface. In the second case the mechanism of the appearance of the *QS* complex (second *QS* type) apparently depends on various amount of living tissue and is therefore determined by several factors: by either a total predominance of the negative intracavitary potential, or predominance of the negative potential of the intramural layer, or by combined influence on the curve of the intracavitary and intramural potentials. The first type was most commonly recorded over the large 'chronic infarct' (the scar), whereas the second type in small fresh foci or on the border of more extensive infarctions.

The *QR* complex was recorded only in transmural infarctions of a mixed structure containing simultaneously living and necrotic or fibrous tissue up to the epicardial layers inclusive. In these cases the *QR* complex was found either in all areas of the affection or along the border of the focus. In subendocardial infarctions *QR* complex was never recorded in the leads from the surface.

Thus, according to Wilson's conception, the initial negative deflection of the monophasic curve, the *QS* complex, is dependent on the transmission to the surface through necrotic tissue of the negative intracavitary potential and is therefore found only in transmural infarction. As Prinzmetal put it, the initial negative deflection of the monophasic curve, the *QS* complex, may depend not only on the intracavitary potential, but also on the transmission of the normal negative intramural potential in affection only of the subepicardial layer. According to both conceptions, the variant of the negative deflection, the *QR* complex, is found in cases of preserved living muscle tissue in the focus of affection, but, in Wilson's opinion, such a complex can also occur in subendocardial infarction, while Prinzmetal holds that this variant is absolutely atypical of subendocardial infarction.

Whatever the mechanism of formation of the negative initial deviation of the monophasic curve, it follows from both conceptions that its appearance in direct epicardial or semidirect precordial leads of the ECG indicates the existence of a necrotic focus in some muscular layer of the heart or its replacement by fibrous tissue.

The conception of the focus of myocardial affection is not exhausted by necrotic or fibrous tissue. Bayley (1942) suggested a scheme of zonal structure of the focus of affection showing that the region of myocardial affection consists of an area of dead

tissue (zone of necrosis), and an adjacent zone of injury which on the periphery passes into the zone of ischaemia.

Three zones reflect various degree of involvement in the focal process of adjacent myocardial areas; each of them may occur in isolation or in any combination with each other. It is practically impossible to establish the true borders between the 'trizonal' focus of affection and the healthy muscle because numerous healthy cells closely interweaving with damaged tissue may be found in the direction of the periphery of such a focus (Sodi-Pallares, 1956).

Each of the three zones is reflected in the ECG. Whereas, according to the two foregoing conceptions, the functionally dead zone corresponds to the initial negative deflection of the monophasic curve, the subsequent course of the curve most commonly in the form of an arched elevation in the *ST* segment embracing the other phases of the ventricular complex is regarded as a function of the zone of injury.

Since the studies conducted by Wilson *et al.* (1933) it has been recognized that prerequisites are created precisely in the damaged cells for incomplete polarization or unfinished depolarization as a cause of the appearance of the current of injury which levels the differentiation of the phases of the *QRST* ventricular complex. Bayley (1942) has shown that in experimental injury to the cell membrane the recorded current of injury creates an electric field comparable to the field of the open layer of dipoles which may be represented by a vector. The field of diastolic current of injury is characterized by a vector directed toward the normal cells. The vector of the systolic current of injury (i.e. the current arising directly after the activation and forming the monophasic curve on the ECG) is directed from the healthy tissue toward the damaged zone. The current of injury indicating the existence of a zone of injury manifests itself on the unipolar ECG as a coarse elevation in the *ST* segment, if it is recorded at the point turned to the incompletely polarized or depolarized region. In the leads located in the opposite positional respect to the given region a depression in the *ST* segment is noted. In the presence of a zone of injury the elevation and depression of the *ST* segment on the ECG is thus regarded as a reciprocal effect of the same current of injury and depends on the orientation of the electrode with respect to the damaged region.

Bayley considers the conception of the 'zone of ischaemia' rather electrically than anatomically. In the zone of ischaemia during diastole the polarization has been already completed, as also in healthy myocardium, whereas during the period of repolarization the beginning of the restoration phase is considerably delayed. If the ischaemic zone is sufficiently large this delay distorts the course of repolarization and the ECG shows the primary changes in the *T* wave. The delayed beginning of repolarization prolongs the electric systole and is the more strongly pronounced the higher the degree of ischaemia. The changes in the *T* wave, as an index of an existence of

ischaemia, are often observed in the pre-infarctional period and often after myocardial infarction. In the acute period of infarction these changes are 'absorbed' by the current of injury or are contoured in a reduced form. According to Bayley, a curve of the ischaemia-injury type shows (despite the general opinion) that the first stage of electrocardiographic evolution of myocardial infarction is the appearance of the primary changes in the *T* wave, which may be considered a manifestation of local ventricular ischaemia.

Thus in focal affections of the myocardium three zones merging into each other are found; their structural and functional peculiarities determine the character of the ECG changes: the necrotic area causes the initial negative deflection of the monophasic curve of the ECG, the zone of injury located around it, an archlike *ST* segment elevation, and the peripheral zone of ischaemia, the *T* wave inversion.

At the same time the necrotic tissue itself creates prerequisites also for finding zones of functional changes. As the experimental studies of Udelnov (1964) have shown, the necrotic tissue determines the appearance of the so-called perinecrotic zone in the region of which functional disorders, including a decrease in the contractile function, may be found over a rather considerable extent. The perinecrotic zone created by the focus of necrosis is characterized by marked electrolytic changes, and also by distortion of the electric function, which is manifested on the ECG by the *ST* segment changes (Kyandzuntseva and Udelnov, 1955; Udelnov, 1955, and Salmanovich, 1959)[1].

The general electrocardiographic diagnosis of focal myocardial affection appears quite simple, if we take into account that in most cases focal affection involves formation of the characteristic monophasic curve. The existing variants of electrophysiological interpretation of the formation of the monophasic curve do not lessen its significance as the chief criterion of the focal process in the heart muscle (according to classic conceptions, all the main ECG changes in myocardial infarction may be consistently explained on the basis of the theory of monophasic oscillations; Presnyakov, 1962). By the monophasic curve, depending on the peculiarities of its form, it is possible with a certain degree of probability to determine in each concrete case the presence of necrosis (initial negative *QS*, *Qr*, *QR* deflection), zones of injury (current of injury-arched *ST* segment elevation absorbing the terminal stage of distorted depo-

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[1] Of late zonality is also found in the focus of affection by histochemical methods. It has been shown experimentally that the level of the decrease in enzymatic activity (dehydrogenases) corresponds to the various degree of disturbance in the mitochondrial structures in the circular zones of the focus. The extent of the latter varies in the first hours and becomes relatively stable 24 hours after the development of the focus of affection (Cox *et al.*, 1968).

larization and at least the initial stage of repolarization) and only sometimes zones of ischaemia (negative, reduced, variously deformed *T* wave). The latter is mainly determined in the leads adjacent to those in which the monophasic curve has been recorded.

It is much harder to judge of the depth of the affection by the monophasic curve. The difficulty lies in the unequal electric functioning of the internal and external layers of the myocardium. The internal layer, as was mentioned above, is the layer of 'electric silence', and only in the subepicardial layer appears and successively increases the main positive *QRS* complex deflection recorded on the surface as the *R* wave. This phenomenon is explained by the fact that owing to the network of the Purkinje fibres which permeate almost the entire subendocardial layer, the conduction in the latter is so intense that excitation embraces almost simultaneously all the areas of the internal layer with the result that only the *QS* complex is recorded at any of its points. In the external layer the impulse is conducted mainly by the muscle fibres and appears more slowly; moreover, with the movement of the wave of excitation toward the epicardium a progressively increased positive deflection (*R* wave) is observed (Sodi-Pallares, 1956). From this it follows that the normal ECG recorded from the surface practically reflects the process of passage of the depolarization wave only along the external layers of the myocardium.

In connection with this the pathological change in the form of the *QRS* complex on the ECG in the leads situated on the body surface is ascribed mainly to the disturbances in the subepicardial layer of the myocardium, whereas the appearance of a single negative *QS* complex may indicate transmural and subepicardial affection.

The changes in the form of the *QR* and its variant (*Qr*, *qR*) depend on the intramural foci in the subepicardial layer with streaks of living muscular tissue persisting above them.

In subendocardial focal affections the ECG does not show an initial negative deflection, while the monophasic character of the curve, when the current of injury merges with repolarization phase, is characterized by a tracing of the current of injury downward from the iso-electric line. However, not the whole subendocardial layer is abundantly supplied with the Purkinje fibres. It has regions where these fibres are either absent or represented very scantily (e.g. the basal parts of the subendocardial layer of the left ventricle). In the period of depolarization such a region normally ensures the reproduction of the *R* wave and, consequently, cannot be ascribed to the region of 'electric silence' (Sodi-Pallares).

The focal changes in the basal parts of the subendocardial layer are attended with formation on the ECG of the *Q* or *QS* wave, like in the affection of subpericardial parts, which, however, is the rarest variant of the ECG changes in subendocardial affection.

In his *Atlas* Zuckermann (1955) outlined clearly enough a scheme of electrocardiographic determination of layer by layer affection,

correlating the zones of affection with involvement in the process of layers of the heart muscle and indices of the ECG recorded from the surface (Fig. 57).

Topical Diagnosis

The ECG method plays an essential role in the topical diagnosis of focal myocardial affection. Neither the clinical picture nor the data furnished by other methods of examination ensure information on the localization of the focus of affection in the heart.

A number of classifications have been suggested for electrocardiographic differentiation of the regions of affection by the focal process. However, even a single focus in the myocardium is rarely limited to some one region. In each concrete case the localization and extent of the focus of affection are determined by the peculiarities of coronary blood supply, the extent of the development of collaterals, etc.

In view of this any classification may be regarded only as a scheme for localizing the affection, from which topical combinations may deviate in the direction not foreseen by the scheme.

The Sodi-Pallares classification (1955), which illustrates the multiplicity of variants of single-focus localization, is characteristic in this respect.

1. Anterior infarctions:
   (a) extensive anterior,
   (b) anteroseptal,
   (c) anterolateral,
   (d) lateral, situated high,
   (e) combined anteroposterior.
2. Posterior infarctions:
   (a) posterior proper;
   (b) posterolateral,
   (c) posteroinferior,
   (d) combined posteroanterior.
3. Infarctions of the interventricular septum.
4. Infarctions combined with right bundle-branch block:
   (a) anterior infarction with right bundle-branch block,
   (b) posterior infarction with right bundle-branch block,
   (c) septal infarction with right bundle-branch block.
5. Infarctions combined with left bundle-branch block:
   (a) anterior infarction with left bundle-branch block,
   (b) posterior infarction with left bundle-branch block,
   (c) septal infarction with left bundle-branch block.
6. Subendocardial infarctions.
7. Right ventricular infarctions.

Despite the seemingly complete list of possible regions of affection and their most common combinations the classification omits a number of forms which most commonly lack specific electrocardiographic manifestations which may reflect the peculiarities of the

given localization or the given combination in the presence of the monophasic curve. Thus not a single heading comprises the affections of the atria, papillary muscles, etc. Nevertheless, in most cases the ECG diagnosis fits in the given scheme.

Modern topical diagnosis of cardiac affections is based on the evaluation of the relations between the changes in the direction of the cardiac vector, as the axis of a single cardiac dipole, which symbo-

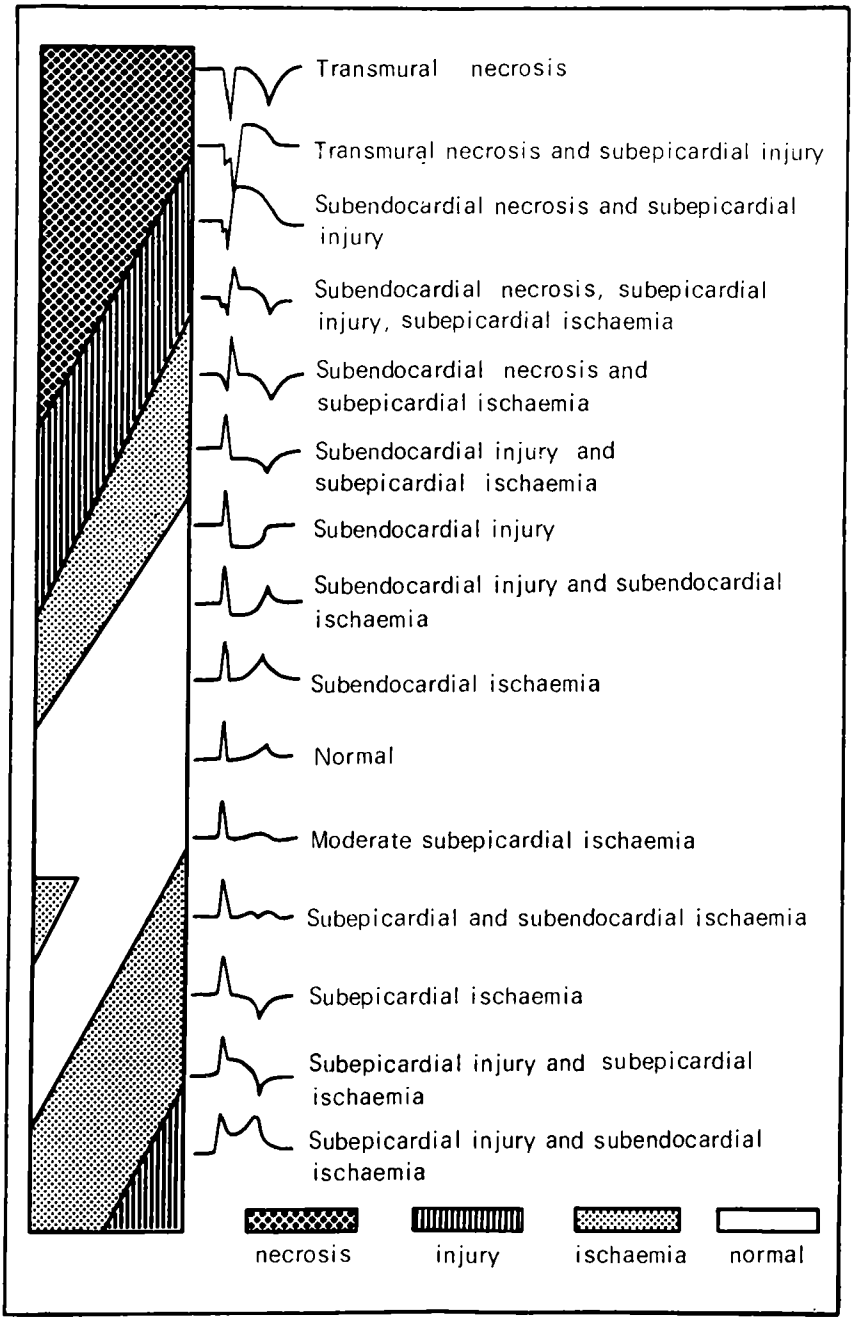

Fig. 57. Reflection on the ECG of the zones of necrosis, injury and ischaemia in focal affection of the myocardium (after Zuckermann)

lizes the processes of depolarization and repolarization, and the axes of the leads recording the vector changes in the system of the generally accepted twelve leads. This is based on the following propositions:

1. It is considered that six leads from the limbs (I, II, III, *a*VI, *a*V*R*, *a*V*F*) are located in the frontal plane and six chest leads ($V_{1,2,3,4,5,6}$) in the horizontal plane (Fig. 58). It follows that by the leads from the limbs it is possible to judge of the vector changes in

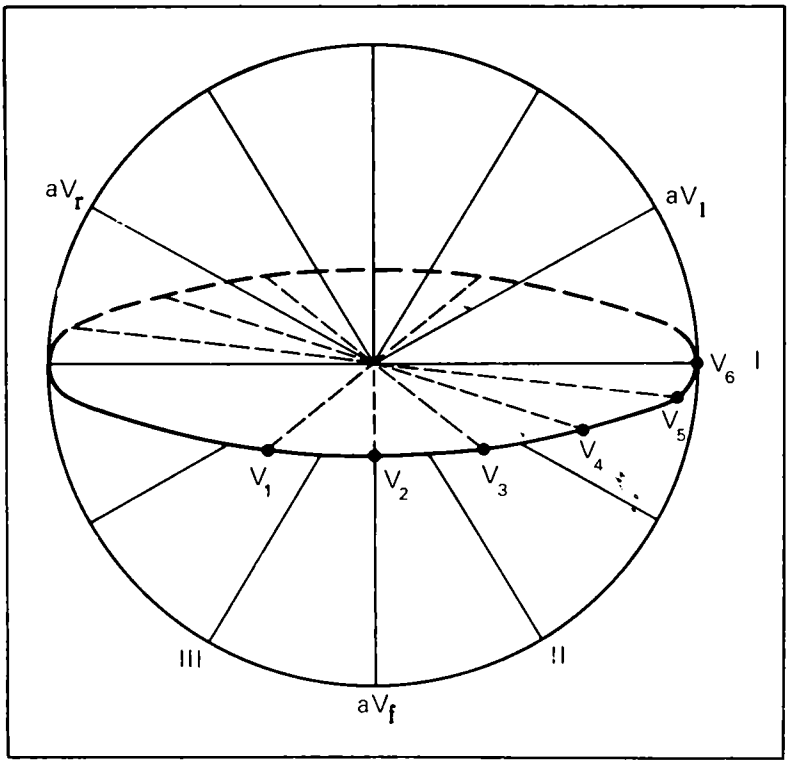

Fig. 58. Combination of two (frontal and horizontal) hexaxial systems of leads (after Lamb)

the superior, inferior, right and left directions, i.e. of the variations of its projection onto the frontal plane, while by the chest leads it is possible to judge of its changes in the anterior, posterior, right and left directions, i.e. of the variations of the vector projection onto the horizontal plane.

2. The proposition of Grishman *et al.* (1952), and Grant (1957) is accepted that the electrically inert (necrotic or scar) tissue deflected the depolarization vector in the direction opposite to the focus of affection. Thus in infarction of the anterior wall the vector is directed backward, in infarction of the posterior wall forward, in infarction of the diaphragmatic (posteroinferior) region of the heart upward, and lateral infarction (of the left ventricle) to the right. This reorientation of the vector in focal changes is accom-

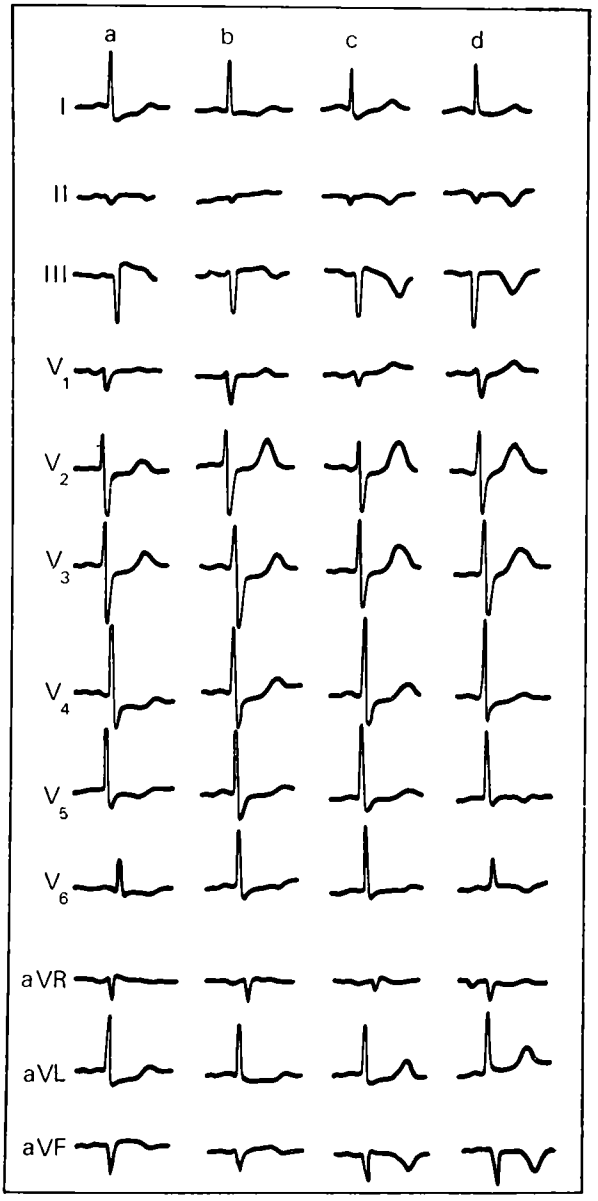

Fig. 59. Main diagnostic stages in the succession of dynamic changes in the ECG *QRST* complex in a vast anterior (involving the lateral wall) myocardial infarction (developed in 54-year-old patient C. in the beginning of April 1966)

a—a stage of the process of rapid formation of the monophasic curve (lead V_3) and its transitional variants (V_2, $V_{4,5}$) on the third day of the disease as a reflection of the existence of a necrotic zone (QSV_3, QRV_4, QRV_5) and the zone of injury (current of injury in lead V_2—V_5);
b—retention of monophase signs in the same leads one week (8/IV) after the beginning of the necrotic process;
c—a stage in the subsequent formation of the pathological two-phase curve with clear differentiation of the second phase in the form of a negative coronary wave *T* (in lead $V_{3,4,5}$ and partly V_2) on a background of regression of the current of injury one month (30/IV) after the onset of the disease, as a reflection of the development of the ischaemic zone around the focus of tissue destruction (process of cicatrization);
d—retention of the same signs of pathological two-phase character without essential changes compared with the preceding curve (*c*) 1.5-2 months (24/5) after the onset of the disease (cicatrization)

panied with registration of the *QS* (*QR*) complex instead of the *qRS* complex in the leads located in the direction corresponding to the given plane.

3. It is taken into account that the appearance of the current of injury is attended with the appearance of the *ST* vector which is oriented in the direction of the zone of injury, if it is located in the subepicardial layer, and in the direction opposite to it, if it is located in the subendocardial layer.

4. An evaluation is made of the variability of the *T* vector whose direction depends on the degree of ischaemia, the extent of the ischaemic zone in depth and along the periphery of the focus, the character

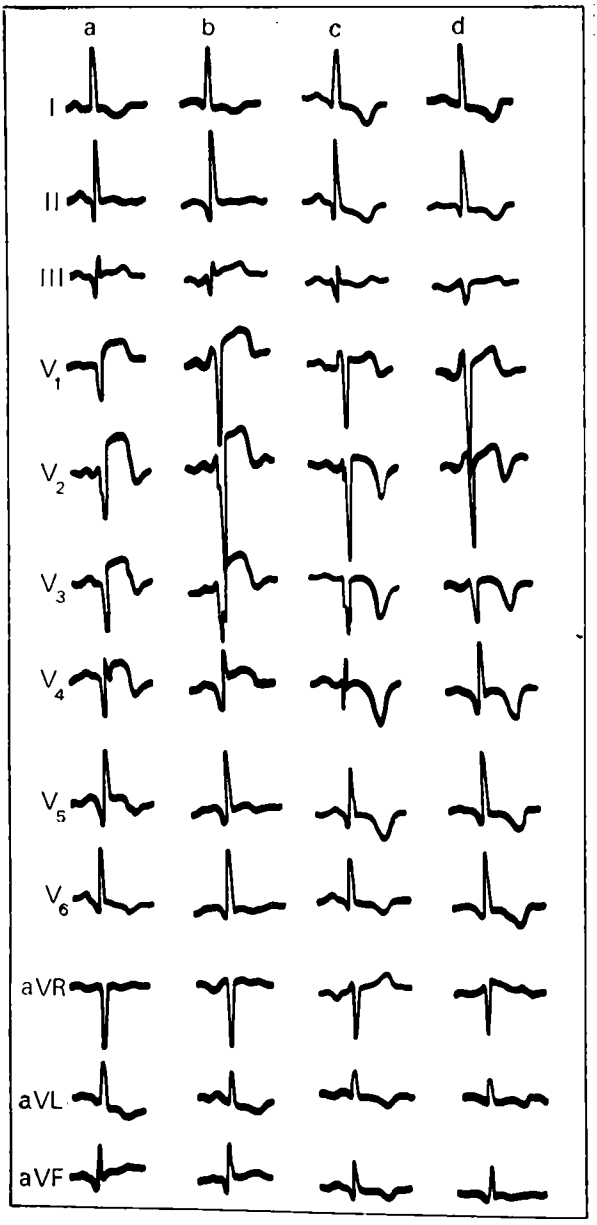

Fig. 60. Main diagnostic stages in the succession of dynamic changes in the ECG *QRST* complex in a posteroinferior (diaphragmatic) myocardial infarction (developed in a 43-year-old patient A. in May 1967)

a—a stage in the process of rapid formation of the monophase curve (leads II, III, *aVF*) 3 days (13/V) after the onset of the disease, as a reflection of the necrotic zone (qs_{II}, QS_{III}, *avF*) and the zone of injury (current of injury in leads II, III, *aVF*; reciprocal downward displacement of the *ST* segment in leads I, V_{2-6}, *aVL*;

b—retention of signs of monophase character in the same leads about 1 week (18/5) after the beginning of the necrotic process;

c—a stage in the subsequent formation of the pathological two-phase curve with a clear differentiation of the negative coronary *T* wave (leads II, III, *aVF* on a background of regression of the current of injury and its reciprocal effect 3 weeks (30/5) after the onset of the disease, as a reflection of the development of an ischaemic zone around the focus of tissue destruction (process of cicatrization);

d—retention of signs of pathological two-phase character and stabilization of the *ST* segment of most leads on the iso-electric level about 1.5 months (20/VI) after the onset of the disease (scar)

and stage of the focal process (according to the vector conception, the *T* vector deflects sideward from the focus of affection, like the deflecting of the initial *QRS* vectors sideward from the focus of necrosis).

These approaches to the ECG diagnosis of focal changes in the myocardium completely apply both to the acute process (infarction), and to the chronic affection (postinfarctional scar, chronic aneurysm). On the ECG an acute process can be distinguished from a chronic one by means of systematic recording of ECGs, i.e. by using the principle of so-called dynamic observation. Essentially only in cases of a single recording the ECG data do not make possible a confident

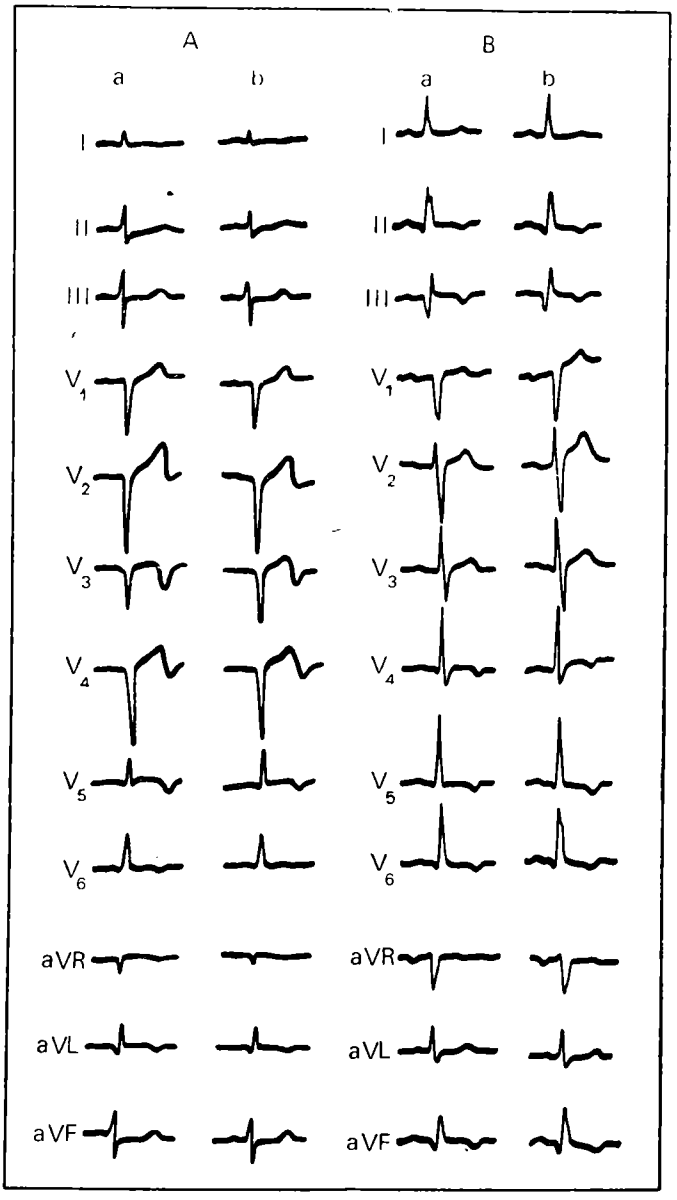

Fig. 61. ECG in a case of focal cicatricial changes in the myocardium

A—ECG of 30-year-old patient K. 1.5 years after vast anteroseptal infarction suffered in January 1968, recorded at a 10-day interval between *a* (13/V 1969) and *b* (22/V); pathological two-phase curve with a permanently altered *QRS* complex in the form of a $QS_{V_2-V_4}$ wave and differently deformed (with minor fluctuations from *a* to *b*) $T_{V_3-V_6}$ wave;

B—ECG of 65-year-old patient G. one year after posteroinferior (diaphragmatic) infarction in spring 1968, recorded at 1 week's interval between *a* (29/IV 1969) and *b* (5/V); pathological two-phase curve with a permanently altered *QRS* complex in the form of qR_{II}, aVF and QR_{III} wave and a negative $T_{II,III}$, avF, V_4-V_6 wave

differentiation between them, especially between acute myocardial infarction and chronic aneurysm.

From the general group of focal affections myocardial infarction differs by a relatively rapid evolution of the ECG from a monophasic to a diphasic curve with different degree of distortion of the recorded depolarization and repolarization phases. This successive

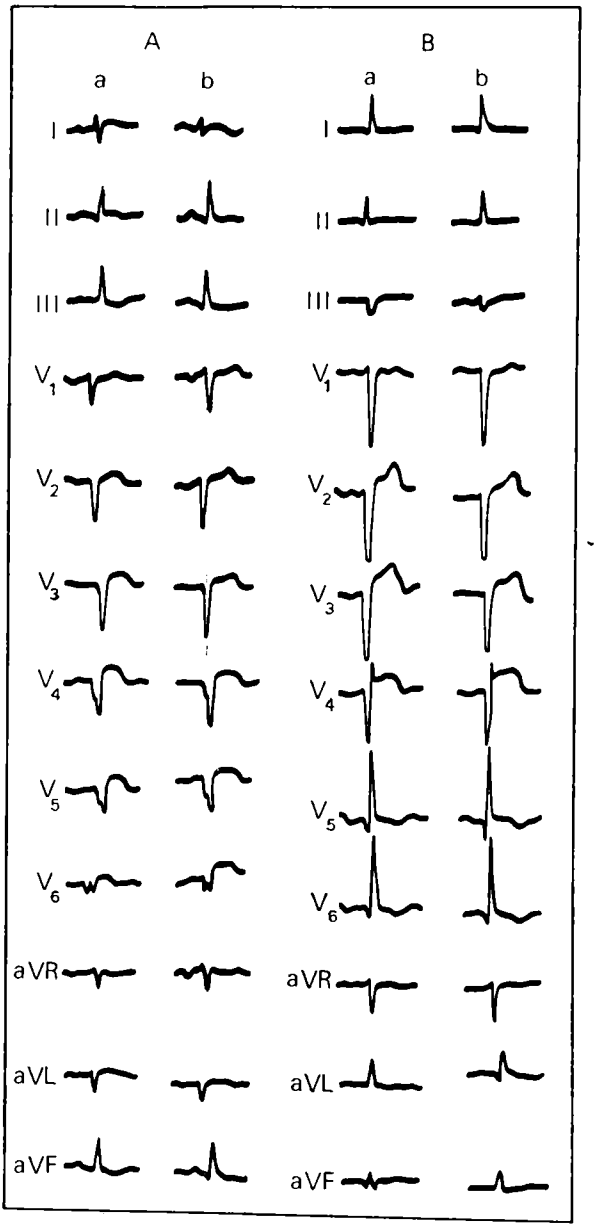

Fig. 62. ECG of cardiac aneurysm

A—ECG of 57-year-old patient G. after vast anteroseptal and lateral infarction (beginning of January 1969) complicated by acute cardiac aneurysm:
a—record of monophase curve (V_2—V_6) after the end of an acute process (25/III 1969);
b—subsequent retention (20/V) of the same ECG morphology ('set' monophase curve);
B—ECG of 52-year-old female patient Zh., after anterosuperior infarction suffered in February 1969;
a—variants of monophase curve (V_3—V_4) after the end of an acute process (29/V);
b—subsequent retention (10/VII 1969) of the same ECG morphology ('set' monophase curve)

transformation of the ECG can be shown only by its systematic repeated registration (Figs. 59, 60). After the expiry of two or three months the *QS* (*Qr*, *QR*) complex persists, nearly as a rule, in at least one or two leads as the most stable trace of a past necrotic process superseded by a scar, while the curve of the current of injury also disappears. The *T* wave inversion (the so-called coronary *T*) formed at some stage of the evolution of the infarction may be regarded only as a relatively stable sign of a past infarction, since it persists only in few persons for a rather long period. In most patients the coronary *T* wave undergoes further considerable changes and often becomes positive, although this process is usually protracted (one year and longer).

The diagnosis of cicatricial changes following an infarction (Fig. 61) is made on the basis of a recorded diphasic curve whose first phase is characterized by a stable deformation of the *QRS* (*QS*, *QR*, *Qr*) complex. This is the main sign of cicatricial changes. The second phase is characterized by multiform configurations of the *T* wave (from negative to positive) in different people. The configuration of the *T* wave may be stable or it may change with time. The *ST* seg-

ment is either on the iso-electric line or is displaced downward as a result of the primary (non-reciprocal) shift owing to ischaemia (Toyoshima *et al.*, 1964) or morphological heterogeneity of the myocardium (fibrosis+normal tissue) which disturbs the temporal relations between the processes of depolarization and repolarization. Unlike the scar in aneurysm, one of the transient variants of the monophasic curve is constantly recorded, but, in distinction to a fresh infarction, in these cases there are no regular shifts in the direction of forming a diphasic curve over a period of many years (Fig. 62).

Rapid regular pattern of the ECG dynamics in the direction of forming a diphasic curve is usually observed in cases of a favourable clinical course of acute myocardial infarction.

In an unfavourable course of the disease, especially in cases which end fatally in the first two weeks, the ECG shows variations within limits of the morphology of the monophasic curve without a marked tendency toward revealing the second phase.

In cases complicated by the development of acute cardiac aneurysm the monophasic curve in some patients is periodically replaced by the diphasic curve and is characterized by variability of separate elements which may change their form over a short period of time without any visible regularity before the ECG is stabilized at the level of one of the variants of the monophasic curve. In other patients, no temporal evolution of the terminal end of the ventricular complex characteristic of acute infarction is observed. In still other patients with acute aneurysm the monophasic curve may exhibit constant contours.

All these cases are quite difficult for electrocardiographic differentiation of acute myocardial infarction from the cicatricial myocardial affection because neither the stability nor the atypical variations of the monophasic curve are an index of the completed process. At the same time the absence of a regular shift toward formation of the diphasic curve does not reflect the usual temporal dynamics characteristic of the course of acute infarction.

In these cases the ECG picture is usually complicated also by the development of various arrhythmias which often replace each other and reflect a disturbance in various functions of the heart (automatism, conduction, excitability) in the most diverse combinations. The picture of acute focal affection may in these cases apparently be differentiated from the severe course of the chronic cicatricial process mainly on the basis of the clinical symptoms and laboratory findings.

With the exception of these cases topical ECG diagnosis of a fresh single infarction is now sufficiently well elucidated in most modern textbooks (Nezlin and Karpai, 1959; Goltsman and Dmitrieva, 1960; Chernov and Kechker, 1966; Dekhtyar, 1966; Kechker and Avrukh, 1966; and others).

The use of the system of twelve electrocardiographic leads makes it possible to approach with sufficient accuracy the determination

of the localization of infarction. The series of studies conducted by Meyers *et al.* (1948) has shown a sufficiently convincing correlation between the ECG changes and the anatomical localization of the focus of affection.

In determining the localization of macrofocal infarction affections of the anterior, diaphragmatic (according to the old terminology, posterior), lateral and septal regions of the left ventricle are roughly distinguished. Involvement of these regions in the focal process is accompanied by the foregoing ECG changes in certain leads: in I, II, *aVL*, V_2—V_4—in the affection of the anterior wall (including the region of the apex), in I, *aVL*, $V_{5,6}$—of lateral, in II, III, *QVF*—diaphragmatic, and in V_1—$V_{2(3)}$—septal regions. At the same time the anatomical localization of infarction relatively seldom pertains only to some isolated region. The focal process usually simultaneously involves the myocardium of the adjacent regions of the left ventricle. In such cases the ECG changes embrace a larger number of leads, e.g. the precordial leads V_1—V_4 in the anteroseptal infarction, leads II, III, *aVF*, V_{5-6} in case of a diaphragmatic infarction spreading to the lateral wall, and other combinations.

Examples of the ECG dynamic changes in the most characteristic localizations of infarction are given in Fig. 58 (extensive anterior infarction involving adjacent regions) and Fig. 59 (posterior diaphragmatic infarction).

At the same time ECG diagnosis of focal affection still contains a number of difficulties pertaining to such forms as microfocal infarctions, subendocardial infarctions, high posterior infarction, periinfarctional block, recurrent and combined infarctions.

1. Microfocal affection of the myocardium is characterized by a relatively favourable clinical course, the ECG changes not typical of focal affection, and a favourable remote prognosis (Holzman, 1955; Prinzmetal *et al.*, 1961; Clagett, 1958; Trushinsky, 1967, and Kozyreva and Petrova, 1968 and others). Microfocal affection of the heart is usually regarded as a transitional or intermediate clinical form between angina pectoris and myocardial infarction (Alekseev, 1958; Lukomsky, 1964 and others). According to Clagett (1958), microfocal infarction occurs in 12.3 per cent of cases of focal affection of the heart.

In addition to this, recurrent microfocal infarctions which have developed on a background of scars resulting from a previous macrofocal infarction are distinguished by the severity and atypical character of the clinical course and are the more severe the shorter the interval between the development of the first infarction and the recurrent one (Popov, 1964), Recurrent microfocal infarction is one of the main variants in the pathoanatomical characteristics of recurrent infarctions.

A primary fresh microfocal affection (Fig. 63) lacks the main ECG criterion of tissue destruction, i.e. there is no initial negative deflection in the *QRS* complex, and no *QS*, *QR* and *Qr* waves. In

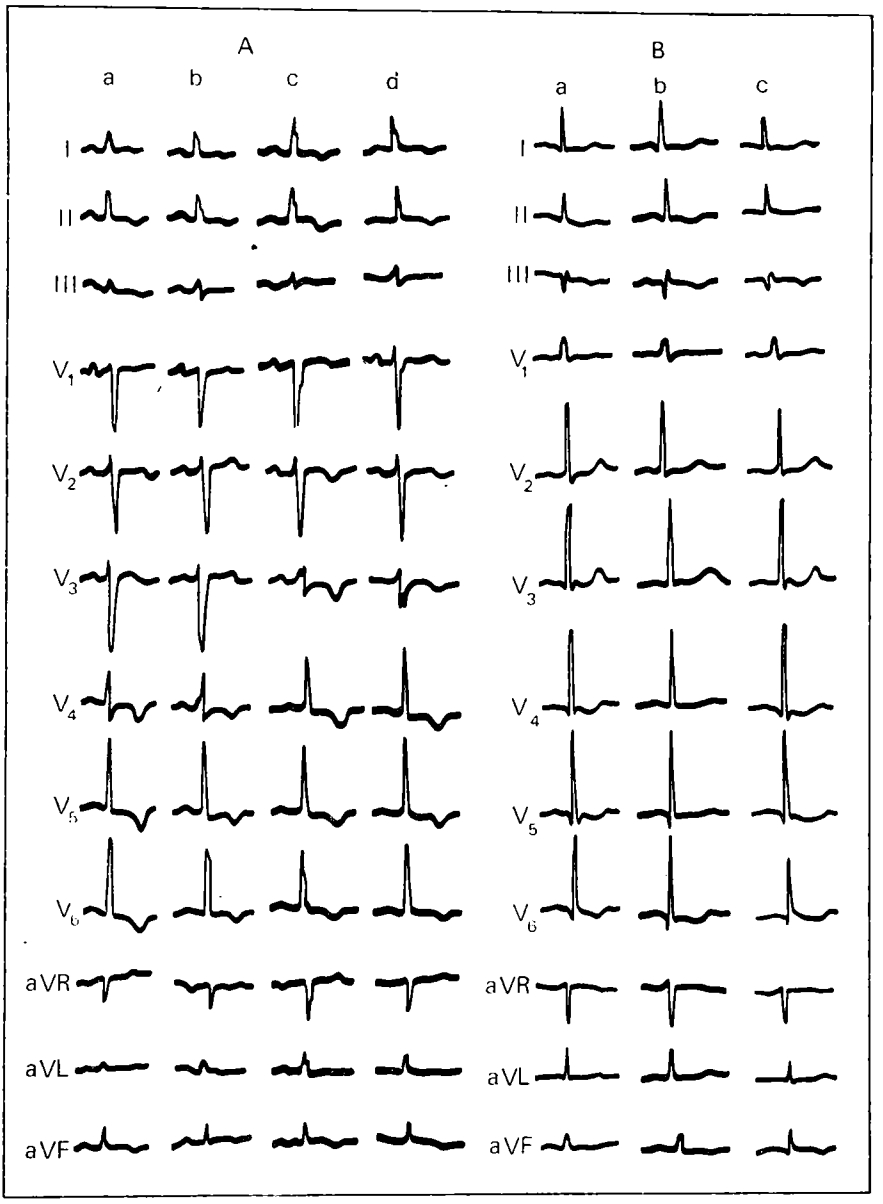

Fig. 63. ECG of acute microfocal myocardial infarction; absence of the stage of monophase curve formation

A—ECG of 51-year-old patient K. with an atypical clinical picture of the course of the disease (June 1969) in an acute microfocal process in the region of the anterior wall of the myocardium;

a—on the day of frequent attacks of angina pectoris (25/VI); pathological (with changes in the terminal part of the ventricular complex) two-phase curve (inversion of the *T* wave in leads II, III, *aVF*, V_4—V_5 and flattening of the *T* wave in lead I);

b—the following day (26/VI); the same two-phase character and a decrease in the RV_6 amplitude;

c—on the sixth day (30/VI); inversion of the *T* wave in most leads (I, II, *avF*, *avL*, V_1—V_6), decrease in voltage and a change in the morphology of the *QRS* complex in V_3;

d—in a week (2/VII); beginning of restoration of the *T* wave (V_1—V_2), increase in RV_6 amplitude, retention of low voltage in deformed *QRS* complex in V_3.

B—ECG of 53-year-old patient B. with an atypical clinical picture of the course of the disease (July 1969) in an acute microfocal process of indeterminable localization;

a—during the period of increasing angina pectoris attacks (7/VII); two-phase curve with changes in the terminal part of the ventricular complex (deformation of *ST-T* in leads II, III, *aVf*, V_4V_6);

b—in 3 days (11/VII); the same two-phase character with a more distinct inversion of the *T* wave in leads II, III, *aVf*;

c—in a week (14/VII); changes in the terminal part of the ventricular complex, repeating the changes in ECGs *a* and *b*, decrease in amplitude of the *R* wave in leads I and V_6, appearance of a small *q* wave in *avF*.

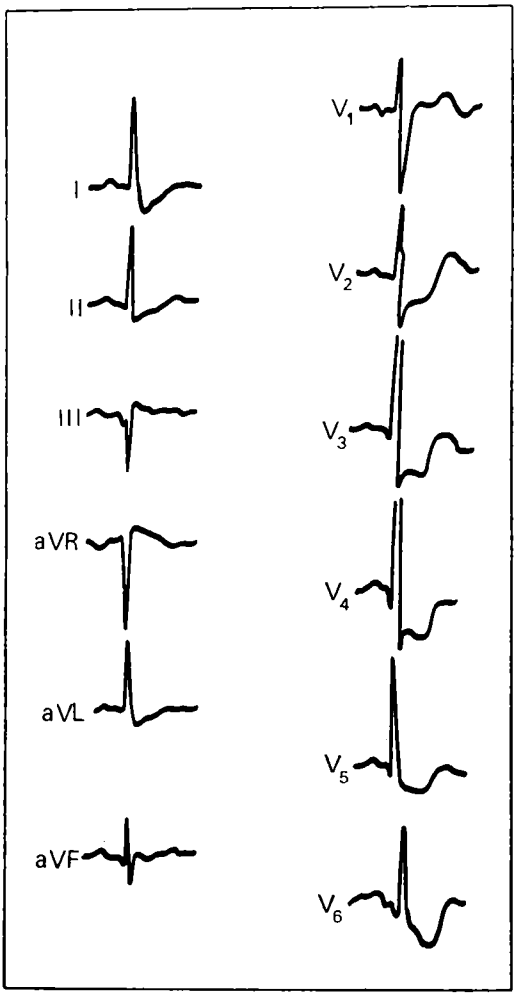

Fig. 64. ECG of an acute subendocardial myocardial infarction in the first hours of the development of a severe attack of retrosternal pain in 64-year-old patient Ch. (October 30, 1968). Monophase curve with its transitional variants recording downward from the iso-electric line in leads from V_3 to V_6

cases where the usual configuration of the *QRS* complex persists a small decrease in the amplitude of the *R* wave is sometimes observed. The *ST* segment may remain at the isoelectric line, but sometimes it shifts upward or downward. The *T* wave is inverted, sometimes assuming the character of the 'coronary *T*' and may also be diphasic. These changes are found in different patients in various electrocardiographic leads. In about half the cases of primary microfocal infarction during the first two months the *T* wave assumes a normal configuration or its negative phase diminishes.

The ECG diagnosis of primary microfocal infarctions requires differentiation from the ECG picture of myocardial ischaemia in stenosing coronary atherosclerosis. The only possible electrocardiographic criterion for differential diagnosis is apparently an evaluation of the stability of the *T* wave inversion; in cases of stenosing atherosclerosis which was accompanied several months before the development of microfocal infarction with the same degree of inversion of the *T* wave as in microfocal affections, it is impossible, unlike the latter, to find any changes toward the ECG normalization (Cutts *et al.*, 1957).

2. The difficulties of ECG diagnosis in subendocardial infarctions (Fig. 64) consist in the fact that destructive changes in the internal layer of the myocardium can be judged only indirectly by the appearance on the curve of signs of injury and ischaemia. The terminal part of the ventricular complex is considerably deformed in the form of a sharp downward displacement of the *ST* segment which often merges with the deformed, sometimes pointed, positive phase of the *T* wave or accompanied with inversion of the latter. In these

cases the normal morphology of the *QRS* complex is preserved with the main positive deflection in the form of the *R* wave.

There are experimental data indicating that, although the initial negative deflection in the form of the *Q* wave is not found in the configuration of the *QRS* complex, in acute experiments reproducing subendocardial infarction the amplitude of the *R* wave may diminish in corresponding leads (Prinzmetal *et al.*). Comparison of ECG changes with autopsy data in extensive subendocardial infarction involving the anterior, lateral, septal and sometimes posterior parts of the left ventricle has shown that in this localization of the affection the *Q* wave is absent, the amplitude of the *R* wave in V_1-V_4 diminishes and the *S* wave appears in V_5-V_6, the *ST* segment in the left chest leads depresses, while in lead *aVR* it is elevated. In cases where the affection has spread further toward the surface, beyond the internal layers, the *QRS* complex was deformed in the leads corresponding to the localization of the process (Cook *et al.*, 1958). In small subendocardial infarctions some depression in the *R* wave, and a downward displacement of the *ST* segment in all or only in the left pericardial leads, and a marked inversion of the *T* wave were observed (Cook *et al.*, 1958). The *T* wave inversion in subendocardial infarction is usually due to ischaemia of the more superficial muscular layers of the heart adjacent to the zone of necrosis (Pruitt *et al.*, 1955).

In practical diagnosis of subendocardial infarction the decreased amplitude of the *R* wave may be taken into consideration only in individual cases where it is possible to compare it with the ECGs of the premorbid period, because there is as yet no mean quantitative criterion for evaluating the degree of the decreased amplitude of the *R* wave, which may characterize subendocardial affection. The chief ECG signs of subendocardial affection are still the depressed *ST* segment and the negative *T* wave. According to our findings, subendocardial infarction may be diagnosed with some degree of confidence in cases where in successive precordial ECG leads with an altered terminal part of the ventricular complex in the first days of the disease at least one lead is found in which the downward displacement of the *ST* segment that merges with the *T* wave completely absorbs the repolarization phase. Such a curve is, as it were, reciprocal, mirror reflection of the monophasic curve characteristic of the affection of more superficial layers. The possible variants of such a reciprocal monophasic curve are shown in Fig. 55.

This type of reciprocal monophasic curve depends not on the orientation of the standard positions of the electrode being studied with respect to the vector of the zone of injury of the superficial layers, but on the directly opposite shift in the direction of the *ST* vector proper owing to the appearance of a zone of injury in the deep layers. In this case the absence of the *QRS* complex deformation indicates that the causal factor of the appearance of the reciprocal current of injury is a disturbance in the structure of the deepest layer,

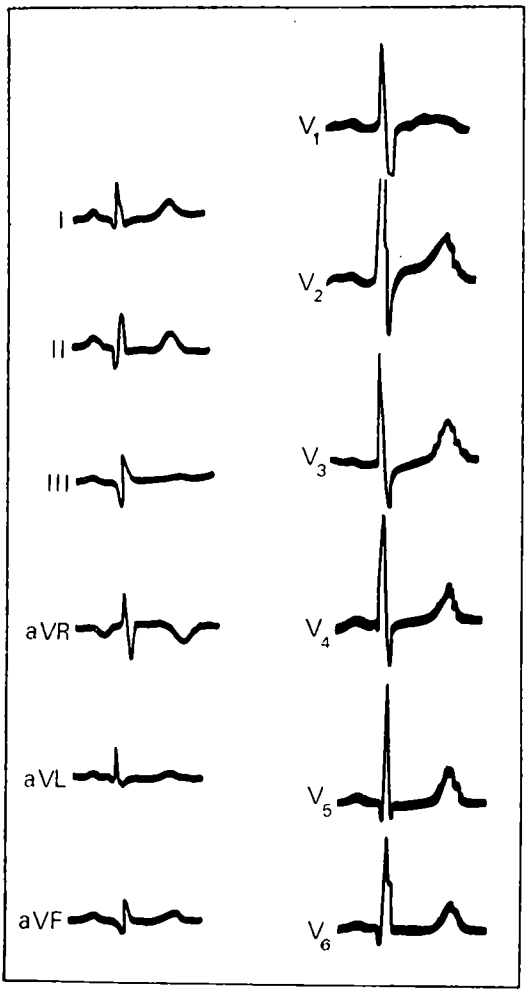

Fig. 65. ECG of 59-year-old patient R., six months (19/V 1969) after an acute myocardial infarction suffered in December 1968. Signs of posteroinferior scar (two-phase curve with a *q* wave in leads II, III, *aVF* and a positive *T* wave pointed at the top) with a possible spread to the upper parts of the posterolateral wall of the left ventricle (high Rv_1 wave)

which does not exert any influence on the course of depolarization in the intact external layers. The decrease in the amplitude of the *R* wave is not a necessary sign in these cases. A sufficiently large *R* wave often persists and in virtue of this requires comparison with the initial curves which in most cases is practically hardly possible. The reciprocal monophasic curve is sufficiently clearly differentiated from the diphasic curve with a primary downward displacement of the *ST* segment accompanied with a *T* wave deformation observed in ischaemia of rather considerable degree and duration without destructive tissue changes (see Figs. 55 and 63, leads V_4-V_6). A further formation of the second phase of the curve in the form of the appearance of a negative *T* wave with a depressed or iso-electric *ST* segment indicates predominance of ischaemic changes in the layers surrounding the focus of affection.

3. A highly situated infarction of the posterior wall or posterosuperior infarction (Fig. 65), also known as high posterolateral or posterior infarction proper (see Sodi-Pallares classification above), occurs rather seldom. Located on the posterior surface of the left ventricle it usually extends upward in the direction of the atria or somewhat to the left, unlike the posteroinferior or diaphragmatic infarction. Different localization of these variants of the posterior infarction determines the unequal deflection of the vector: the diaphragmatic (posteroinferior) focus deflects the vector mainly upward or to the left, which is recorded by the electrocardiographic leads situated in the frontal plane (*Q* waves in leads II, III, *avF*), whereas the posterior focus proper (posterosuperior) deflects the vector predominantly forward and somewhat to the right, i.e. mainly perpendicularly to the frontal plane, in virtue of which the deflection of

the direction of the vector is not recorded by the standard leads, but can be noted in the chest leads located in the horizontal plane (high R wave in V_1-V_2 or q wave in V_7-V_9) (Scherlis *et al.*, 1951; Tulloch, 1952; Elek *et al.*, 1954; and Rothfeld *et al.*, 1961). However, owing to the low voltage of the *QRS* complex in the posterior chest leads and normally it is not always possible to find the q wave, while the appearance of a tall R wave and V_1 is typical not only of posterosuperior infarction, but also of hypertrophy of the right ventricle and certain forms of block of the right branch of the bundle of His. On the other hand, the direction of the T wave in V_1 cannot be regarded as a criterion since in this lead it may be positive or negative also in healthy people. Electrocardiographic differentiation between posterosuperior infarction and hypertrophy of the right ventricle proves practically impossible. This pertains particularly to cases of progressive cardiovascular failure in atherosclerotic cardiosclerosis in which the appearance of a tall R_{V1} may be conditioned equally by both causes.

A number of recent studies have shown that such differentiation can be made to a certain extent by vector cardiography (Rothfeld *et al.*, 1961; Tranchesi *et al.*, 1961, and others). In posterosuperior infarction the vector cardiography shows increased, delayed, directed forward and to the right initial parts of the spatial loop with a preservation in a horizontal plane of the normal counterclockwise direction of a loop record (Grishman's system). In a right ventricular hypertrophy the recording of the curve of the horizontal plane often changes and assumes a clockwise direction. Thus overall electrocardiographic study makes it possible to reveal the syndrome of posterosuperior infarction, namely, tall R_{V1} with a positive T_{V1}, an increase and forward shift of the initial part of the *QRS* loop, a normal counterclockwise loop record in Grishman's horizontal plane. In this case some authors (Rothfeld) explain the delay in the initial part of the loop by peri-infarctional disturbance in conduction.

4. In recent years the problem of the ECG diagnosis of focal affection has attracted the attention of researchers by the question of the so-called peri-infarctional block which is characterized by a change in the vectors of the last 0.04 sec of the depolarization period (Fig. 66). According to Grant (1957), the elements of peri-infarctional block can be found in half of all the cases of infarction attended with deformation in the initial parts of the ventricular complex. Peri-infarctional block is revealed mainly in cases of focal affection (predominantly of the anterolateral wall) in combination with one of the variants of parietal block.

There are two explanations of the ECG picture in peri-infarctional block (Grant). According to one conception, the radial spread of excitation is blocked by the focus of affection on the way from the endocardium to the epicardium, in virtue of which the wave of excitation reaches the epicardial layers located over the foci of affec-

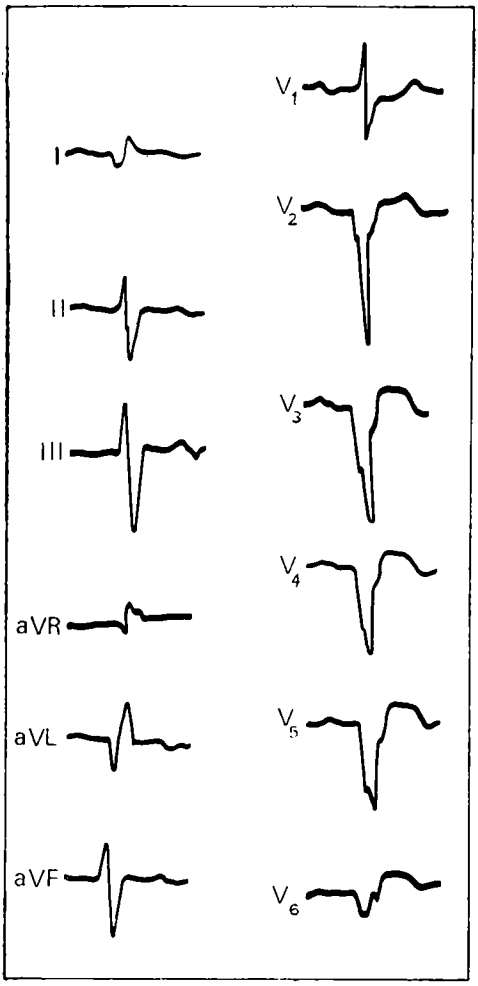

Fig. 66. ECG of 55-year-old patient Kh. (11/I 1963) with signs of an aneurysm of the anterolateral wall of the left ventricle and a possible peri-infarctional block. "Set" monophase curve in leads from V_3 to V_6 with a *QS* complex from V_2 to V_6 after myocardial infarction suffered in 1962. Broad, deep *S* wave in leads II and III with a normal duration of the *QRS* complex. Sharp deflection of the mean electric axis of the heart to the left owing to the prevailing value of the S_{III} wave ($<\alpha=-95°$)

tion by a more round about way and depolarizes them last. According to the second, more widespread opinion, the peri-infarctional block arises as a result of organic affection (fibrosis) of the conduction system of the left ventricle proper on the way of the bifurcation of the peripheral anterolateral branch of the bundle of His.

The ECG signs of peri-infarctional block are characterized by summation of the signs of parietal block and focal affection: (1) a sharp deviation of the electric axis of the heart to the left and its shift of up to 30° and more or a divergence in the direction of the initial (middle) and terminal vectors of depolarization within the limits of 110-180°; (2) a contouring of the *Q* wave in the leads characterizing the localization of the focus (First *et al.*, 1950; Grant, 1957, and Banta *et al.*, 1964). The duration of the *QRS* complex may be normal, reach or exceed 0.11 sec. According to some opinions, the duration of the *QRS* complex depends on the extent of affection of the conduction pathways located parietally; slight fibrosis in the region of the conduction pathways does not cause a noticeable temporal shift in the ventricular complex of the electrocardiogram and vectorcardiogram, while moderate fibrosis determines the delay of the terminal part of the *QRS* loop of the vectorcardiogram; total fibrosis of the anterolateral branch prolongs both the *QRS* complex of the ECG and the *QRS* loop of the vectorcardiogram (Libanoff, 1964).

5. Until recently the most difficult problem in ECG diagnosis of myocardial infarction has been that of recurrent infarctions and foci of combined localization (Fogelson, 1957; Lukomsky and Tareev, 1957; Popov and Gvatua, 1957). According to Glukhova and

Sokolova (1968), in focal affections of the myocardium the ECG diagnosis fails to coincide with the pathoanatomical data in nearly 30 per cent of cases, of which 26 per cent are recurrent myocardial infarctions. This is apparently due to a considerable polymorphism of the ECG picture in cases where a new focus is superimposed on the old scars. In connection with this it is very difficult to systematize the ECG changes in recurrent infarctions. It should be noted that the characteristic ECG dynamics determined by a fresh focus of necrosis may be greatly distorted or completely levelled by old cicatricial changes and, on the contrary, in cases of the appearance of new necrotic areas the signs of old myocardial scars sometimes disappear.

At the same time each of the two or several foci of affection may have zones of necrosis of a different or an equal extent, injury and ischaemia, may involve in the pathological process various or the same layers of the myocardium and be localized in the same or different regions of the heart.

According to Popov (1964), the character of ECG changes in recurrent myocardial infarctions depends on certain factors, namely, the number of infarctions survived by the patient, the extent and localization of both the new and previous myocardial infarction, the duration of the interinfarctional interval, the character of the initial ECG on a background of which the signs of the new infarction are formed, and others.

The clinical classification of recurrent myocardial infarctions suggested by Popov shows the whole complexity of the dynamic evaluation of the ECG recorded in order to reveal the signs of a fresh process. According to this classification, the following clinicoanatomical variants of recurrent myocardial infarction are distinguished:

1. Recurrent macrofocal myocardial infarction:
   (a) usual course,
   (b) protracted variant,
   (c) relapsing variant.

2. Recurrent microfocal myocardial infarction:
   (a) usual course,
   (b) relapsing variant.

It is quite obvious that the character of the ECG dynamic changes, even in a relatively simple case of macrofocal recurrent infarction running a usual course, will be distorted. In such cases the ECG deformation will not always exactly correspond to the classical conceptions of the zonality of the fresh focus and affection of a definite layer of the myocardium, because it reflects the summation of the pathological signs of two processes differing in time. In these cases there is no parallelism between the evolution of the ECG changes

and the course of myocardial infarction. Thus superimposition of the current of injury on the *ST* segment previously displaced downward may lead to its elevation to the iso-electric line, which without a sufficiently deep analysis of the clinical picture may be regarded as a sign of the 'ECG normalization'. On the other hand, the appearance under the same conditions of reciprocal current of injury owing to a fresh subendocardial process may intensify the downward displacement of the *ST* segment and then, in the absence of changes in the initial part of the ventricular complex, the ECG may be evaluated as an index of 'deterioration of myocardial blood supply owing to chronic coronary failure'.

The appearance of a positive initial deflectioin in the right chest leads in posterosuperior infarction on a background of the preceding *QS* complex in any leads is most commonly evaluated as a manifestation of signs of right ventricular hypertrophy, if only the ECG picture is taken into account. Many such examples may be cited.

Shishkin (1963) generalized the diversity of ECG changes in recurrent infarctions in three main variants: (1) new changes appearing in the acute period completely camouflage the signs remaining in the ECG after the first infarction; (2) the ECG signs of recurrent infarction are completely camouflaged by the changes retained in the ECG in the cicatricial period following previous focal affection; (3) the ECG retains sufficiently distinct changes remaining after the first infarction, and new changes connected with the recurrent infarction are superimposed on them.

Electrocardiographic diagnosis of recurrent focal changes, especially topical diagnosis, is possible only in the third variant, whereas the first two variants apparently determine the considerable percentage of divergencies between the electrocardiographic and pathological and anatomical data.

The same difficulties arise in simultaneously developing fresh foci in opposite regions, e.g. in the posterior and anterior walls of the left ventricle.

A comparison between the electrocardiographic and autopsy data in focal affections of the myocardium made by Glukhova (1966) has shown that in a fresh combined affection of the anterior and posterior walls the ECG signs of posterior infarction are revealed in the cases where the focal process in the anterior wall is limited to the subendocardial layer. If the anterior infarction embraces the entire thickness of the myocardium (transmural affection) the ECG signs of the simultaneously developing posterior infarction are not revealed. In most cases of fresh posterior infarction arising on a background of extensive scars in the anterior wall the ECG is dominated by distinct signs of the posterior infarction, while the signs of the anterior scar decrease, but do not completely disappear. In cases of the development of fresh transmural focal affection of the anterior wall on a background of extensive scars in the poste-

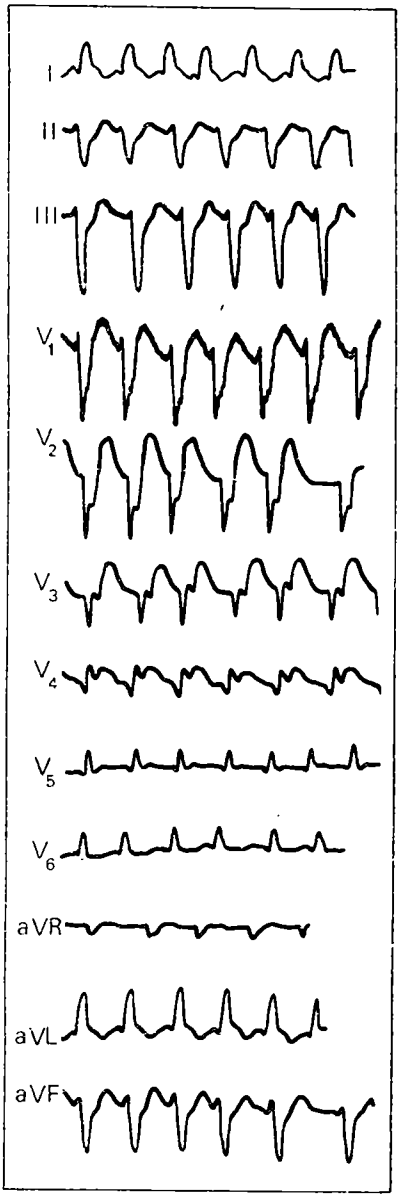

Fig. 67. ECG of 71-year-old patient V. with anteroseptal and apical myocardial infarction recorded on March 12, 1965, and recurring one year after the first postero-inferior infarction (January 1964). Monophase curve in V_2—V_4. Complex rhythm disturbance: tachyarrhythmic form of atrial fibrillation; transitory period of atrial flutter 1 : 1 (see lead *aVL*); left bundle-branch block ($QRS = 0.14$ sec)

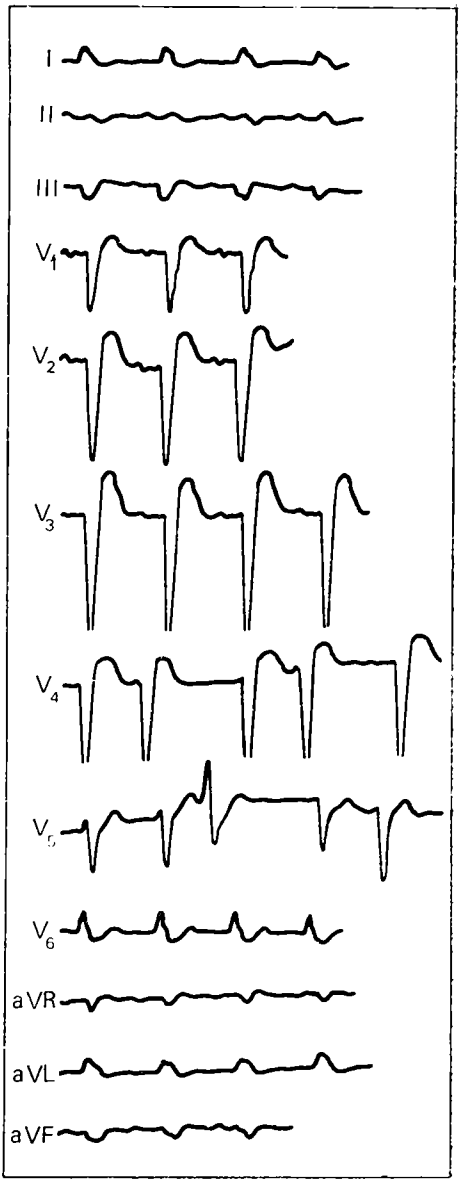

Fig. 68. ECG of 46-year-old patient G. with anteroseptal and apical myocardial infarction. Monophase curve in V_1—V_4. Complex rhythm disturbance: period of atrial extrasystolic bigeminy (see lead V_4). Single ventricular extrasystole (see lead V_5). Arborization block ($QRS = 0.16$ sec)

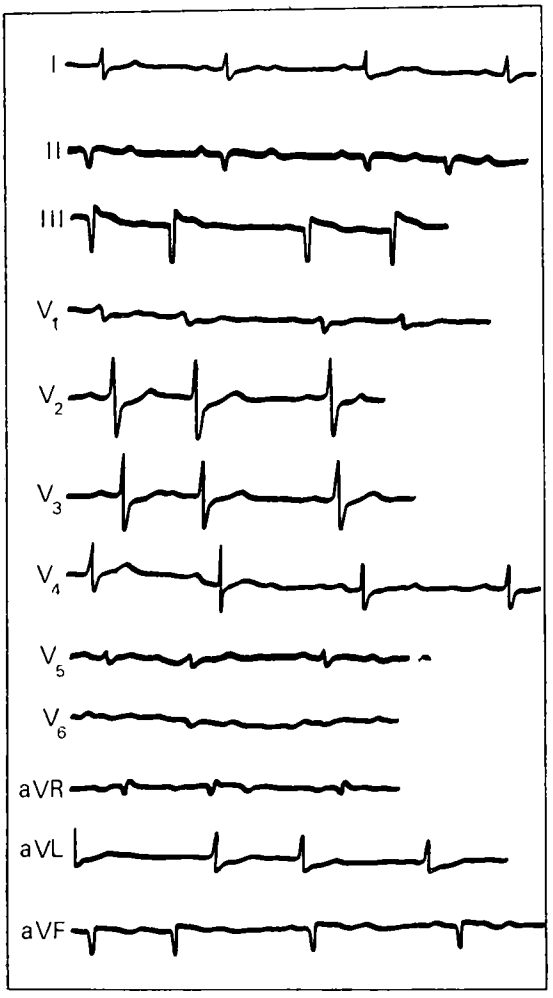

Fig. 69. ECG of 64-year-old patient L. with postero-inferior myocardial infarction recorded on March 22, 1966 and recurring 3 years after the first infarction (1963) of the lateral wall. Variants of monophase curve in leads II, III, *aVF* (and V_6?). Low voltage of the *QRS* (*qrs*) complex in lead V_5. Complex rhythm disturbance: alternation of II (Wenckebach-Samoilov period 3:2 with successively increasing prolongation of the *PQ* interval) (see leads III, V_1—V_3, etc.) and III (dropping out of every other ventricular complex; see leads *T*, V_4, etc.) degrees of disturbances in atrioventricular conduction (A. L. Myasnikov's classification)

rior wall the ECG signs of the posterior scar completely disappear and signs of fresh infarction of the anterior wall are found.

According to a certain point of view, the electrophysiological mechanism of manifestation of the ECG changes in combined focal affection of various regions of the heart depends on the degree of asymmetry of the foci of affection in the myocardium (Kyanzhuntseva and Udelnov, 1955, and Popov, 1964).

The different forms of arrhythmias observed in many patients in the course of acute myocardial infarction do not reflect the specific influence of the focus of affection on the disturbance only in some particular function of the heart. The clinic has long since known that in myocardial infarction any form of arrhythmic activity of the heart, may be found more or less frequently in the same patient including complex arrhythmias, and combinations of disturbances in several functions of the heart, which are often diagnosed only by electrocardiography (Grotel, 1940; Lukomsky, 1943; Shestakov, 1951; Makolkin, 1957; Goldberg, 1968, and others). The examples of some disorders of the rhythm accompanying the development of acute myocardial infarction are shown in Figs. 67, 68 and 69.

The manifestation in each individual case of myocardial infarction of the predominant disorders of such cardiac functions as automatism, conduction and excitability apparently depends on: (1)

the individual threshold sensitivity of the anatomical structures of the myocardium; (2) the character and extent of pathological changes in the functional state of the contractile myocardium and the conduction system under the influence of other pathological processes preceding the infarction; (3) the simultaneous involvement in the process of the arterial branches supplying the different levels of the conduction system; (4) the individual reactivity of the central and vegetative parts of the nervous system. The size of the focus of affection is of some significance to the arrhythmic cardiac activity in the sense that the deeper and more extensive the focus the higher the probability of the summary influence of these, mainly individual, prerequisites for the disturbances in the physiological functions of the heart as a result of infarction.

The connection between the localization of infarction and the disturbance in various functions is not always clearly traced. The opinions on this question found in literature are contradictory. In any case, a disturbance in the function of conduction always impels a suspicion of the involvement in the process of the septal region. However, a monophasic curve in the extreme right chest leads is considered a direct ECG sign of focal affection of the septum, while a disturbance in conduction is a similarly indirect criterion of its involvement in the process as a simultaneous recording in the ECG of signs of infarction of anterior and posterior localization. But also as an indirect sign the disturbed conduction does not necessarily indicate a destructive process proper in this region. It may in the same measure also reflect functional disorders resulting from transient ischaemia in the zone of the conduction system, especially on the atrioventricular border (Chernogorov, 1962). It is assumed that in such cases ischaemia of the septal region develops either because of a spasm of the arterial branches supplying the conduction system that accompanies the affection of the main vascular trunk, or as a result of the spread of ischaemia, that surrounds the main focus to the interventricular septum, which may be dependent on the peculiarities of cardiac vascularization. The significance of the involvement of the conduction system in the perinecrotic zone is also not excluded (Salmanovich and Udelnov, 1955).

Upon the appearance of conduction disturbances the suspicion of septal infarction arises in cases when (1) a block of one of the branches of bundle of His or a high degree of atrioventricular block, which indicates involvement of the posterobasal part of the septum, appears in the period of the development of myocardial infarction; (2) the ECG picture of total block of the right branch of the bundle of His is accompanied with a formation of the *Q* wave in the right chest leads, while that of the left branch of the bundle of His is accompanied with a formation of the *Q* wave in the left chest leads, or by a decreased voltage of the left chest and standard leads (Osher and Wolff, 1953).

In cases of a *QRST* complex deformed owing to a longitudinal block (especially that of the left branch of the bundle of His) it is not always possible to find the main ECG sign of a focal affection, i.e. the monophasic curve in the corresponding leads, which renders topical diagnosis particularly difficult. A number of authors suggest the use of the indirect criteria of focal affection in these cases: the disturbance of the regular pattern of the changes in the size of the *R* wave in successive chest leads, dissociation of the changes in the standard and chest leads, and an elevation in the *ST* segment with transition to the tall *T* wave in certain leads (Fogelson, 1957; Tartakovsky, 1958; Kilinsky *et al.*, 1959; Tumanovsky *et al.*, 1968).

According to Sumarokov (1965), ectopic arrhythmias occur in 20 per cent of patients with acute myocardial infarction and considerably deteriorate the prognosis. Continuous (monitor) electrocardiographic control in the acute period of the disease (Chazov and Ruda, 1967) shows that in myocardial infarction arrhythmias develop more frequently and are of paramount prognostic importance. The prognosis is the least favourable in cases where a combination of three and more forms of rhythm disturbances persists for more than two or three days after the onset of acute myocardial infarction (Goldberg, 1968).

In most cases such ectopic arrhythmias as atrial extrasystole, nodal extrasystole and nodal rhythm issuing from the superior and middle part of the node of Ashoff and Tawara, migration of a pacemaker in the limit of the sinus and atrioventricular nodes, atrial fibrillation and supraventricular paroxysmal tachycardia do not prevent the formation and discovery on the ECG of the monophasic curve, i.e. the main diagnostic criterion of the heart muscle destruction.

On the other hand, the ventricular forms of ectopic arrhythmias, which distort the succession of the spread of excitation over the myocardium, of themselves cause a coarse deformation of the ECG ventricular complex. In ventricular extrasystole, however, the characteristic features of the ECG indicating the development of myocardial infarction may be found in the complexes which correspond to sinus impulsation. Neither single ventricular extrasystoles nor an allorhythmic succession of their appearance can therefore essentially prevent the ECG diagnosis of a fresh focal process. At the same time the diagnosis is complicated in the group, especially polytopic, ventricular extrasystole, which frequently develops in severe cases of infarction and paroxysmal ventricular tachycardia. In these cases the discovery of a monophasic curve in dynamic electrocardiography depends upon the duration of the period of arrhythmias. The greatest difficulties are encountered in interpreting the changes in the ECG elements in acute myocardial infarction in cases of stable idioventricular rhythm with a complete transverse block. Nevertheless, the ECG diagnosis of focal affection may be complicated in

any form of the arrhythmic cardiac activity, most commonly with combined disturbances in the different functions of the heart (Fig. 66), a diversity of combinations of ectopic arrhythmias with various forms and degrees of the disturbance in conduction (Fig. 67), the absence of regular pattern of the consecutive character of the transition of one degree of disturbance of a particular function to another (Fig. 68), and a number of other peculiarities of manifestation of arrhythmic cardiac activity.

8

TREATMENT

One of the most important achievements of Soviet cardiology is elaboration of methods of treating myocardial infarction patients. In organizing the system of treatment Soviet researchers have for the first time solved a number of scientific and methodological problems and have thereby made a considerable contribution to the world science. These successes are in a considerable measure due to the fact that in solving this problem it was possible successfully to combine the advanced methods of organization of medical service existing in our country with the latest achievements of science.

In organizing the most effective and rational system of treatment of myocardial infarction patients not only representatives of medical science took part but also organizers of public health service. The system was being improved by a mass of medical practitioners, especially first-aid doctors. The introduction of new methods of organization of medical aid to myocardial infarction patients, extensive utilization of modern methods of diagnosis and new methods of treatment have resulted in a decrease in mortality from myocardial infarction.

In studying the statistical data concerning the mortality from myocardial infarction it is possible to distinguish two periods in the course of which the mortality decreased. The first period pertains to the thirties-forties, when the diagnosis of myocardial infarction became the property not only of experienced clinicians, but also of polyclinical doctors in connection with the thorough studies of its clinical picture (especially its effaced forms) and wide use of the electrocardiographic method. The relatively mild affections of the myocardium and microfocal necroses began to be more widely diagnosed, which contributed, on the one hand, to a seemingly in-

creased incidence of myocardial infarction, and to a decreased mortality, on the other. The latter was, to course, largely due to the introduction of new methods of treatment. An examination of the monographs of those years, especially dealing with myocardial infarction (Grotel, 1940 and Gelstein, 1948), shows that many propositions were introduced into therapeutic practice which are used in the treatment of myocardial infarction today: a sparing regimen, indications (also cautious) on the necessity of wider use in some complications of strophanthin, quinidine, etc. However, the main reason for the decreased incidence of mortality from myocardial infarction in those years was, in our opinion, an increased number of milder forms of the disease owing to achievements in diagnostics.

The second period of decrease in mortality began after 1956. It was characterized by the development of new organizational forms and extensive introduction of new methods of treating myocardial infarction. Heparin, cardiac glycosides (strophanthin and corglycon), sympathomimetic amines for treating cardiogenic shock, novocainamide for treating disturbances in rhythm, etc. became more widely used.

Every year brings something new to the therapy of myocardial infarction. Recommendations for using steroid hormones to treat shock appeared in the beginning of the sixties; fibrinolytic enzymes (fibrinolysin, streptokinase), potentiation anaesthesia with nitrous oxide for analgesia began to be used in 1961-1962, and, somewhat later, electro-impulse therapy for arrhythmias connected with myocardial infarction, antifoaming agents, urea, Lasix (frusemide) in the treatment of pulmonary oedema, etc. The use of ganglioplegics and auxiliary blood circulation for the treatment of cardiogenic shock has been discussed of late. The appearance of new methods of treating myocardial infarction and its complications could not but affect the mortality from this severe disease. However, many of the foregoing methods are also used in the treatment of myocardial infarction by foreign authors who, at the same time, report a much higher death rate that do Soviet researchers.

What are the reasons for this difference? In our opinion, an important role was played, in the first place, by the main organizational principle of treatment now adopted in the USSR and consisting in early hospitalization of myocardial infarction patients. Its importance comes particularly clearly to the fore in cases of severe, complicated forms of the disease.

Hospitalization of Patients

One of the main principles of treating myocardial infarction patients adopted by Soviet cardiologists is their early hospitalization. It is known that the appearance of myocardial infarction is often accompanied with a number of complications which not only ag-

gravate its course, but frequently also lead to fatal results. Thus of the 230 per cent patients who died of myocardial infarction A. V. Vinogradov observed single or repeated collapses in 44.3 per cent of cases. According to Shestakov, thromboses or embolisms occurred in 76 of the 457 cases, 40 of the patients having died. The observations conducted in our clinic with automatic recording of the ECGs have shown that arrhythmia of various type occurs in 90 per cent of myocardial infarction cases, nearly in 60 per cent of them it lasts up to several hours and longer. At the same time, the death rate among them is nearly 15 per cent higher than in uncomplicated cases. Of the 420 myocardial infarction patients whom we personally observed heart failure developed in 44 per cent, the lethality thus increasing the death rate in the group almost threefold.

The success of treating complications largely depends on how soon the patients are given complete and highly qualified medical aid. Moreover, the modern methods of treatment (defibrillation, nitrous oxide anaesthesia, administration of fibrinolytics and anticoagulants, cardiac glycosides and antiarrhythmic agents, etc.) require perfect clinical and diagnostic equipment.

The acute period of myocardial infarction must proceed under constant control of a physician because precisely this period is fraught with fatal complications, disturbances in rhythm in the first place.

The foregoing was the prerequisite that determined the development of the Soviet organizational scheme of treating myocardial infarction patients, recognized today as the best in world medical practice.

1. Organization of specialized first-aid teams equipped with special transport and apparatus and staffed with well-trained specialists. The organization of these teams pursued the aim of bringing highly qualified medical aid to the myocardial infarction patient in order that all the methods of treatment may be used, especially in complicated myocardial infarction cases, from the very first hours of the disease. The importance of this stage of treatment was emphasized by Meddox, President of the International Cardiological Society, who said that mortality in myocardial infarction is high because the patients remain without appropriate highly-qualified treatment during the most dangerous period of the disease. It is the merit of Soviet physicians that they have made highly-qualified aid available to the patients. The new methods of treatment together with their progressive organization make it possible convincingly to improve the prognosis in myocardial infarction. Of some importance is also the decrease in the period of time between the onset of the disease and the hospitalization.

2. Early (in the first hours) hospitalization of the patients.

3. Organization of specialized departments, 'centres' of treating myocardial infarction patients, well equipped and staffed with highly-qualified personnel.

4. Organization of a system of rehabilitation.

Only under hospital conditions is it possible to administer complete necessary treatment and ensure sufficient medical observation with the use of new clinical and diagnostic apparatus, cardiomonitors in particular. Despite the fact that most leading cardiologists expressed their opinion in favour of such tactics of treating myocardial infarction patients and it was reflected in the decisions of the Fourteenth All-Union Congress of Internists there were apprehensions concerning the possible increase in mortality during transportation and the prognosis for patients hospitalized in the first day of the disease.

More than ten years have passed since the method of early hospitalization began to be introduced into the practice of the health service. Thousands of patients hospitalized in the first hours or days of the disease have been observed during this time. Some conclusions can be drawn, considering that there is as yet no such system of treating myocardial infarction patients abroad or that, for example, in Czechoslovakia, the GDR, and England, it is only beginning to come into existence.

First of all, concerning the mortality during transportation.

The apprehension that the transportation of patients will negatively affect the course of myocardial infarction and will increase the incidence of mortality have not been confirmed. The transportation of myocardial infarction patients in specially equipped ambulances after carrying-out the necessary measures at home (administration of heparin, mesatone or noradrenaline [norepinephrine] in cases of collapse, conduction of nitrous oxide anaesthesia and neuroleptoanalgesia in cases of a severe pain syndrome, etc.) does not affect the mortality of myocardial infarction patients. According to Novikova *et al.* (1965), there was not a single fatal case in Sverdlovsk ambulances during the five years of work of specialized teams which transported 8000 patients.

The safety of transportation of myocardial infarction patients is also confirmed by the experience of the Moscow City First-Aid Station. During 1960-1964 specialized teams administered first aid to 6256 myocardial infarction patients, four of them having died in ambulances (Vinogradov *et al.*, 1965).

Considerable data have been accumulated on first aid administered to myocardial infarction patients by the Leningrad First-Aid Station. The data (Filipchenko *et al.*, 1961) confirm the safety of transportation of patients in the acute period of myocardial infarction. According to Zilberman (1967), in Kiev, for example, only four patients died in ambulances over a period of five years.

Organization of specialized teams in the first-aid system has played an important role in decreasing mortality from myocardial infarction. By administering complete modern treatment of myocardial infarction (and its complications) both at home and during transportation the specialized teams largely determine the favour-

able results of the disease. For example, the use of Antifoamsilane (Simethicone, antifoam A, mylicon, silain) as an antifoaming agent by Rudneva, on our suggestion, in pulmonary oedema under first-aid conditions considerably improved the prognosis in this complication of myocardial infarction. A rapid positive effect was obtained in 35 of the 38 cases. Our method is now been extensively used in administration of first aid.

According to Zilberman (1967) (Kiev First-Aid Station), introduction of electro-impulse therapy into practical work of first-aid teams resulted in normalization of the rhythm in 88.3 per cent of cases. It should be particularly emphasized that an important role is played by the specialized first-aid system in the treatment of patients with cardiogenic shock. The effectiveness of the treatment of this complication of myocardial infarction depends on how soon it is begun. This is why the work of a first-aid physician determines to a considerable extent the prognosis in this complication. It is difficult to compare the effectiveness of the treatment in various groups of patients where much depends on the severity of cardiogenic shock, the time of the beginning of treatment, etc. However, all the authors who were engaged in the problems of its treatment under first-aid conditions (Belkin, 1961; Zilberman *et al.*, 1955, and Smetnev, 1966) noted a considerable decrease in mortality. In Kiev, for example, among the 235 hospitalized patients with cardiogenic shock it amounted to 37 per cent, while in one of the groups in Moscow (1964-1966) it decreased to 46 per cent.

The organization of specialized departments for the treatment of myocardial infarction patients is also very important. Such departments have special wards equipped with necessary diagnostic and therapeutic apparatus where intensive, i.e. continuous, control of the cardiovascular functions is carried out (Fig. 70). According to our observations conducted in one of Moscow's hospitals, mortality from myocardial infarction in the hospital as a whole decreased to 15.5 per cent, whereas in a specialized department with the same contingent of patients in a grave condition it amounted to 8 per cent.

Today the importance of organizing specialized centres for treating myocardial infarction patients in large cities is no longer doubted. Organization of such a centre at the A. L. Myasnikov Institute of Cardiology (USSR Academy of Medical Sciences) resulted in a decrease in mortality among myocardial infarction patients from 26.4 per cent in 1962 to 16.2 per cent in 1968. It should be emphasized that, according to the severity, these groups were almost the same. Ganelina *et al.* (1970) report that in a ward of intensive observation organized by them the mortality decreased from 33 per cent in 1966 to 23 per cent in 1968. According to Goldsman and Day (1965), the organization of a specialized department resulted in a 50 per cent decrease in mortality.

It should be pointed out that it is not enough to name a department 'specialized'. A decrease in mortality may be achieved only

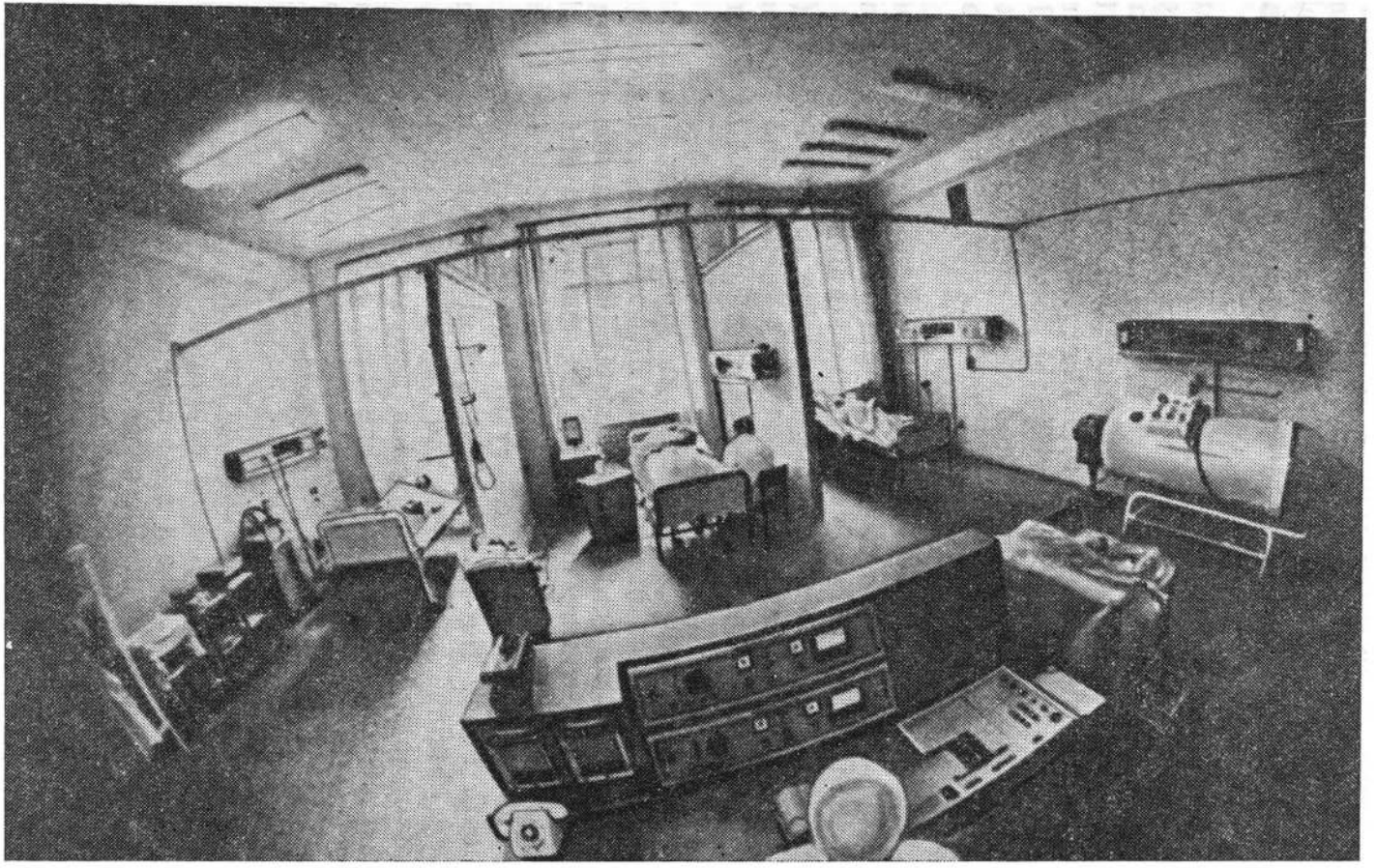

Fig. 70. Interior of the intense observation ward at the A. L. Myasnikov Institute of Cardiology (Photograph by S. Lidov)

if this department is staffed by specially trained highly-qualified personnel, is equipped with the necessary apparatus and employs all modern methods of therapy. Continuous medical observation must be carried out in shock division of this centre. We agree with Lown *et al* (1967) that all people working in these departments must aim their efforts primarily at preventing the possible complications of myocardial infarction rather than providing for reanimation.

Reanimation plays a definite role in the work of these departments, but prevention of complications is of a much greater importance as it is more important, by using novocainamide (procainamide), lidocaine (lignocaine, DDA) or other anti-arrhythmic agents, to eliminate ventricular extrasystole than to administer electroimpulse therapy in connection with the subsequent ventricular fibrillation. It is more significant and easier to organize correctly the treatment with fibrinolytics and anticoagulants than to treat thromboembolic complications.

To evaluate the effectiveness, expedience and safety of the method of early hospitalization of myocardial infarction patients, it was necessary first of all to conduct comparative studies of the course of the disease in cases (1) when the patients were admitted early; (2) in more remote periods after the onset of the disease and (3) when they were treated at home. Such studies were carried out by a number of authors.

Comparative evaluation of the data on prognosis and mortality in myocardial infarction involves many difficulties associated with the peculiarities of the contingent of hospitalized patients, the qualification of the attending physicians and the potentialities of the treatment. Moreover, in studying the mortality of myocardial infarction patients at home it is necessary to take into account cases of sudden death before the medical aid was given. Very interesting results were obtained by Kalinina and Bogoslovsky (1964) who studied the fate of myocardial infarction patients on the territory of the Bauman district of Moscow. Among the 373 hospitalized patients there were nearly two times less fatal cases than among the 316 patients treated at home. This difference is particularly significant as regards patients 40-49 years of age; of them 7.3 per cent died in hospital and 34.5 per cent at home (Fig. 71).

This difference may perhaps be explained, on the one hand, by the fact that younger patients most commonly fail to observe the regimen of rest, especially in the absence of adequate control which can be organized only in hospitals. On the other hand, in the acute period of myocardial infarction complications develop which require active action on the part of a physician

Several reports are now available which contain comparative data on the treatment of myocardial infarction patients at home and in hospitals. Thus 40 per cent of patients treated at home and 22 per cent of those treated in hospitals died in Odessa in the course

of nine months in 1965. In Krasnodar the mortality amounted to 35 per cent among patients treated at home and only to 21.5 per cent among those treated in hospitals (Chazov, 1965).

Interesting data were obtained by Krister *et al.* (1964) who studied mortality from myocardial infarction in Kiev in 1962. It appeared that in 1962 many more myocardial infarction patients were hospitalized than in 1960 (32.9 per cent in 1960 and 63.3 per cent in 1962). At the same time, hospital mortality increased (28.7 and 34.5 per cent, respectively). The reason for it was that the hospitals began to admit seriously ill patients who formerly died during the

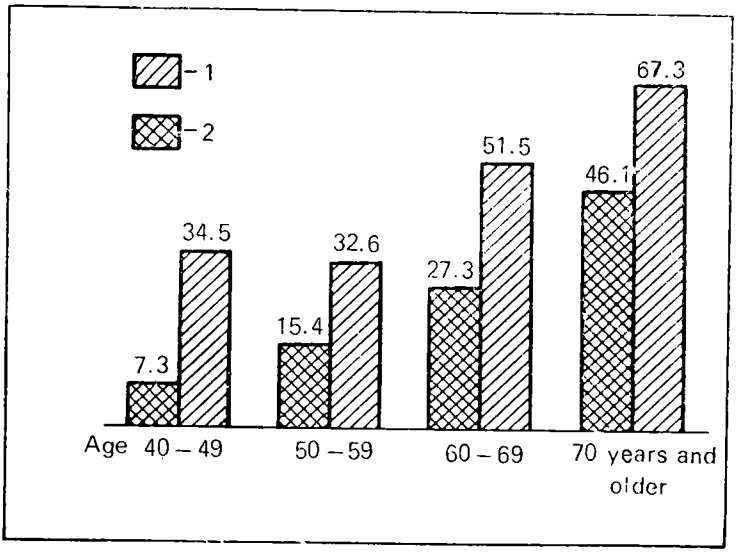

Fig. 71. Death rate among myocardial infarction patients treated at home (*1*) and in hospital (*2*)

acute period at home. At the same time, however, the total mortality from myocardial infarction in Kiev considerably decreased (from 43.4 to 38.2 per cent) owing to decreased mortality at home (from 49.5 to 35.8 per cent). In the first three days of the disease 32.9 per cent of patients died in the hospitals of Kiev and 49.2 per cent at home. Similar data are cited by other authors. For example, Martynkin (1962) (Leningrad) reports, that whereas mortality among the patients examined by him and treated at home amounted to 56 per cent, among those hospitalized at an early period it was only 18.2 per cent.

All the foregoing proves that the patients can be adequately treated, especially during the acute period, only in hospitals. The observations, in which the course of the disease of patients hospitalized during early periods, i.e. in the first hours and days of myocardial infarction, were compared with those hospitalized at much later periods, confirm the necessity of hospitalizing myocardial infarction patients as early as possible. Such tactics make it possible

to provide proper treatment during the severest period of the disease which largerly accounts for the high mortality from myocardial infarction.

Analgesia

The first thing which the doctor encounters at the bedside of a myocardial infarction patient is a persistent pain attack which must be quickly eliminated not only because all pain requires relief, but also because it may cause the development of shock.

In its nature pain is the organism's protective reaction which warns about a danger. Signalling a disturbance in the normal function of an organ or tissue it impels the patient to take measures at eliminating its cause. This applies particularly to pain of coronary origin in which case it indicates myocardial ischaemia. Later, as Orbeli (1936) pointed out, pains may cause disturbance in the function of various organs and provoke secondary painful phenomena. Of some importance here are also changes in the central nervous system (Anokhin, 1957), in the function of endocrine organs, especially the hypophysis (Danilov, 1941), and the adrenals (Selye, 1967) and, finally, biochemical changes in various organs and tissues. They are particularly dangerous to patients with coronary failure in whom the compensatory capacities are diminished not only of the heart and vessels, but also in various regulatory systems. This may explain why in the overwhelming majority of patients with cardiogenic shock (97 per cent), whom we observed at the Institute of Cardiology, the latter developed precisely on a background of an intense pain attack.

Over a long period of time narcotics[1)] (morphine or pantopon) were the only effective means of controlling pain. The history of using opium preparations, which include morphine and pantopon, numbers hundreds of years. Some mechanisms of their analgesic effect are now well known. Most authors associate the effect produced by these preparations with the action on the central nervous system, the zone of the optic thalamus and the cerebral cortex (Zakusov, 1953; Wilker, 1950, and others).

Numerous clinical observations show that in most cases of acute coronary failure the pain attack may be terminated only by repeated (in some cases only intravenous) administration of narcotics. For example, of the 80 patients in whom the course of the pain syndrome was thoroughly studied, in eight the effect occurred after administration of 2 ml of a 2 per cent promedol (trimeperidine) solution, in 16 after one injection of a 1 per cent pantopon or morphine solution, in 25 after two injections of the same dose, while 19 required more than two injections and to 12 the narcotics had to be injected intra-

[1)] Here and subsequently in designating analgesics of the opium group the term 'narcotics' is used because it is widely employed in practical medicine.

venously. Thus it follows that in most cases a positive effect was produced by administration of substantial doses of narcotics, i.e. more than 2 ml of a 1 per cent pantopon or morphine solution.

There are various opinions on the use of narcotics for analgesia in myocardial infarction. It is believed that morphine not only eliminates pain, but under its influence the sense of fear and anxiety disappears, a peculiar euphoria takes place, which is very important for preventing and treating shock phenomena in the acute stage of myocardial infarction (Gelshtein, 1951; Balotin, 1959; and others).

Most authors recommend to begin the treatment with subcutaneous injections of 10-20 mg of morphine and, if it proves ineffective, to repeat them every 30-40 min. Some authors point out the necessity for intravenous injection of morphine, if it is not sufficiently effective when administered subcutaneously (Blumgart, 1954, and Sumarokov, 1965).

At the same time, it is known that alkaloids of opium, especially in large doses, in addition to a favourable analgesic effect, produce also a number of side effects which may aggravate the course of the disease. For example, according to Agress and Binder (1957), and Hochrein and Schleicher (1963), large doses of narcotics may be conducive to a decrease in arterial pressure. Moreover, excitation of the vomiting center and the vagus, and inhibition of the motor and secretory activity of the gastro-intestinal tract may negatively affect the course of myocardial infarction and forster the development of complications. Cases are known of paresis of the gastro-intestinal tract and the urinary bladder, and dynamic impatency of the intestines associated with their use. In order to prevent such complications morphine or pantopon are usually administered in combination with 0.5 ml of a 0.1 per cent atropine solution which removes the side effects produced by these substances on the smooth muscles.

Morphine and pantopon inhibit the respiratory center, especially when injected intravenously. A decrease in pulmonary ventilation, the minute volume of respiration and the sensitivity of the respiratory centre to carbon dioxide, which are noted when morphine is used, may deteriorate the course of myocardial infarction.

In addition to the side effect produced by narcotics, which is directly reflected on the clinical manifestations of the disease, morphine or pantopon may affect some of the biochemical and physiological processes of the organism. The experimental findings of Kudryashov *et al.* (1964) have shown that morphine depresses the 'organism's' defensive anticoagulation system and increases the tendency toward thrombogenesis. These findings were confirmed by the clinical observations of our coworker Iosava (1965). On administering 1 ml of a 1 per cent morphine solution he observed in 11 of the 15 patients an increased plasma tolerance for heparin (26 ± 3 min before administration, and 20 ± 2 min after). The time R in the thromboelastogram decreased (from 14 ± 2.7 to 11.5 ± 2.8 min

after administration of morphine). All this confirms the experimental findings that the thrombogenic properties of the blood increase upon administration of narcotics. Administration of large doses may give rise to, or aggravate, the acidosis, which is characteristic of myocardial infarction. Whereas experimental injections of small doses of morphine even for a long time do not disturb the acid-base balance (Alekseev and Pushkareva, 1956), large doses sharply decrease the alkaline reserve of the blood already in 20-25 min (Starkov, 1950).

We not only concur with V. N. Vinogradov and his associates on the necessity of 'sparing morphine', but also believe that with the modern methods of analgesia its use in myocardial infarction must be reduced to the minimum. It is probably expedient, considering the high analgesic activity of morphine, to begin analgesia in a severe status anginosus by administering the narcotic in usual doses and, in the absence of a sufficient and rapid effect, to resort to other forms of analgesia. The 'economy of morphine' is obtained by using other substances which exert much less of a negative influence on the course of the pathological process.

Introduction of nitrous oxide into the treatment of pain syndrome in myocardial infarction is undoubtedly a big contribution of Soviet cardiology. Nitrous oxide used for anaesthesia for about 150 years has a valuable property in that not being a protoplasmic poison it does not produce any toxic effects on various organs and tissues. It physically quickly saturates the tissue spaces and rapidly leaves them by being excreted unchanged by the lungs. For example, toward the end of the second minute after cessation of inhalation 78 per cent of the gas is eliminated from the organism (Frumin *et al.*, 1961). In a concentration of less than 80 per cent nitrous oxide does not affect the respiratory centre, does not inhibit the circulatory centres and does not stimulate the vomiting and coughing centres. It is important to emphasize that before the onset of the narcotic effect it is possible to observe a certain degree of obtused pain sensitivity; moreover, in low concentrations of the narcotic this state is maintained throughout the whole period of inhalation of the gas. In equal concentrations with oxygen nitrous oxide does not depress consciousness, while reducing pain sensitivity.

The Soviet authors are pioneers in the use of nitrous oxide in therapeutic practice and, what is particularly important, in treating pain syndrome under conditions of first aid. By using the portable gas-anaesthesia apparatus developed in the USSR (today the AH-8 model is widely used) Sergeev showed as far back as 1954 that under conditions of first aid the mixture of nitrous oxide and oxygen effectively alleviates angina pectoris and the pains connected with myocardial infarction. Most of the patients noted a rapid disappearance of the pain sensations. In 1961 Petrovsky and Efuni reported on many hours' analgesic anaesthesia produced in conditions of a hospital for a therapeutic purpose. The extensive experience of

using a mixture of nitrous oxide and oxygen for various diseases, including pain syndrome in myocardial infarction patients, was generalized for the first time. In the course of a few minutes the authors managed to relieve such severe pain attacks that could not be terminated even by repeating administration of narcotics. One more important aspect of this report should be emphasized. The authors used with a very good effect the so-called method of self-anaesthesia in angina pectoris. The essence of it is that the patient takes the mask of the anaesthetic apparatus himself and inhales a mixture of nitrous oxide and oxygen in a ratio established beforehand. When the patient stops inhaling the mixture the apparatus is automatically switched off. Today this method is finding increasingly wider application.

There are many reports not only on the considerable effectiveness of the given method of controlling the pain syndrome, but also on its peculiarities and influence on various aspects of metabolism and the functions of various organs. And finally, the most rational combinations of nitrous oxide with other analgesics have been elaborated (Sukhinin, Chuchkalov, Belkin, Smetnev, and others).

In recent years following the example of Soviet authors, nitrous oxide has also been used in many other countries (Czechoslovakia, the FRG, England, etc.). Iosava of the Institute of Cardiology carried out a large series of studies of the most effective methods of analgesia in myocardial infarction. A comparative study of various methods of analgesia was conducted on extensive clinical material (close to 300 patients). The safety of the mixture of nitrous oxide and oxygen in myocardial infarction was demonstrated first of all. We used nitrous oxide with oxygen for more than 24 hours in 12 cases, and observed no side effects even in a single case. Nor did the patients become habituated to this anaesthetic. For example, patient C. with myocardial infarction complicated by pericarditis had to inhale it daily for about four or five hours every day over a period of 28 days, for which purpose 20 000 litres of nitrous oxide were used. We did not find either side effects or any changes in the acid-base balance and thrombogenic properties of the blood.

Iosava made a thorough study of the various indices of thrombogenesis in the use of nitrous oxide in the clinic and noted a marked increase in blood fibrinolytic activity. Before anaesthesia fibrinolytic activity averaged 328 ± 31 min, according to Kaulla and Schultz, whereas after anaesthesia it increased to 263 ± 24 min. The data of thromboelastogram indicated a decrease in the tendency of the blood toward thrombogenesis (the time increased from $4.5 \pm \pm 0.24$ to $6.2 \pm \pm 1.2$ min, while the value E decreased from 118 ± 5.5 to 102 ± 9.6). Thus, nitrous oxide anaesthesia did not negatively affect the indices of the thrombogenic properties of the blood. On the contrary, as a result of its administration, the tendency toward thrombogenesis decreased.

Study of the influence of anaesthesia induced by a mixture of

nitrous oxide and oxygen on the indices of the acid-base balance of the blood was similarly important. It turned out that the anaesthesia caused no essential changes in the tension of carbon dioxide (pCO_2 46.9±0.58 mm Hg before and 46.1±0.59 mm Hg during anaesthesia). The acid-base balance was normalized; this was also indicated by the changes in the standard bicarbonates the content of which increased from 20.2±0.83 to 23.2±0.72 mM/l.

It should be emphasized that we do not deny the possibility of changes in thrombogenesis and the acid-base balance of the blood during anaesthesia in connection with the disappearance of pains which may of themselves cause changes in the aforesaid systems.

The effectiveness of three methods of anaesthesia using nitrous oxide—single component, combination of nitrous oxide and analgesics (promedol) and potentiated—was studied at our Institute. The scheme of single component anaesthesia consisted in induction of analgesia with nitrous oxide and oxygen:

The first five min O_2	100%
The next 5 min $N_2O:O_2$	80%:20%
The next 10-15 min $N_2O:O_2$	70%:30%
The next 15-20 min $N_2O:O_2$	60%:40%
Subsequent anaesthesia $N_2O:O_2$	50%:50%

This scheme was compiled with due regard for a number of prerequisites. By prescribing pure oxygen we proceeded from the necessity of the patient's adaptation to the mask and respiration under new conditions; we also pursued the aim of inducing anaesthesia more rapidly because inhalation of pure oxygen fosters the replacement of the nitrogen of the alveolar air and prevents dilution of nitrogen by the anaesthetic mixture in the period of induction of anaesthesia (Miles *et al.*, 1956). Heller and Watson (1962) also reported a positive role played by a transient preliminary inhalation of pure oxygen before administering high-percentage nitrous oxide. In elaborating further stages of anaesthesia we proceeded from the studies of Artusio (1954) and Federmesser who distinguish three levels of anaesthesia. They suggest induction at first of a deeper anaesthesia with its subsequent weakening to the stage of analgesia. It is considered that, to achieve the third level of anaesthesia, where the verbal contact is completely lost and mental perception is excluded, it is necessary to inhale 75 per cent of nitrous oxide for a period of 3-4 min, whereas for moderate analgesia 50 per cent concentration is enough.

Our experience shows, however, that effective and rapid analgesia is achieved only in half the patients when the single-component anaesthesia is used. The effectiveness of another method was therefore studied, in which the main anaesthetic, nitrous oxide, was combined with small doses of morphine or pantopon, and most commonly with a synthetic analgesic—promedol. Synthesized in the USSR, promedol has now for a rather long time been used as an analgesic in therapeutic practice, including the treatment of myocardial in-

farction (Gefter and Matusova, 1955; Dovgyallo, 1957, and others). Largely devoid of the side effects characteristic of opium preparations (excitation of the vomiting center, depression of the motor and secretory functions of the gastro-intestinal tract) it produces, however, a much weaker analgesic effect. But when it is induced on a background of nitrous oxide the results are better than when only promedol or nitrous oxide are used. Multicomponent anaesthesia has increased the effectiveness of the analgesic measures in myocardial infarction and made it possible to achieve success in 70-75 per cent of cases. The clinical aspects of this method in myocardial infarction, as Iosava has shown, have a number of peculiarities. First of all, it is a more rapid onset of such a level of anaesthesia which leads to the loss of verbal contact with a patient. Nausea and vomiting appear rather more often than in a single-component anaesthesia. The absence of effect in a number of cases and side effects in some patients in the form of excitement and vomiting impelled us to seek other ways of enhancing the effectiveness of nitrous oxide anaesthesia. As is known in anaesthesiology the potentiation principle is widely used. In pharmacology the concept of potentiation (augmentation) in administering several medical substances has existed for a long time (Kravkov, 1907; Nikolaev, 1948, and Zakusov, 1953).

All forms of combined anaesthesia are probably potentiated in principle, but in anaesthesiology this term designates the combination of anaesthesia and neuroendocrine block.

In myocardial infarction potentiated anaesthesia envisages the use of nitrous oxide, on the one hand, and administration of neuroplegics, on the other, and has a number of peculiarities. It is primarily the striving to avoid deep neuroplegia which is, as a rule, accompanied with a very protracted and uncontrollable inhibition of the organism's adaptive and compensatory capacities. In the Institute of Cardiology we mainly used two substances—aminazin (chlorpromazine) and pipolphen (promethazine). Aminazin potentiates and prolongs the action of analgesics, hypnotics, sedatives and general anaesthetics (Sadove *et al.*, 1954; Haas, 1958; Kruglov, 1958; Mashkovsky, 1967). The action of aminazin is connected with its influence on the region of the hypothalamus and the reticular formation. Aminazin possesses central adrenolytic, marked antivomiting and antihistaminic action (M. D. Mashkovsky and other authors).

It is necessary to emphasize the marked antivomiting action of aminazin, which is particularly important in cases of myocardial infarction involving dyspeptic phenomena. According to some authors (Kaverina *et al.*, 1958), aminazin is capable of dilatating the coronary vessels and of improving coronary circulation, which must also favourably affect the course of myocardial infarction. All these positive properties of aminazin made it possible to suggest it for the treatment of the pain syndrome (Sukhinin and Chuchkalov,

1958). We specially studied the effect of aminazin on the pain syndrome connected with myocardial infarction. It appeared that in 17 of the 21 cases, where the usual doses of promedol failed to produce an analgesic effect, 1 ml of a 2.5 per cent aminazin solution administered together with 1 ml of a 2 per cent promedol solution produced a positive effect. Sukhinin and Chuchkalov (1958) noted an analgesic effect of aminazin in 8 of 12 myocardial infarction patients. Thus the combined therapy with aminazin and small doses of narcotics produces an analgesic effect even without nitrous oxide in a considerable percentage of myocardial infarction patients. The analgesic effect of nitrous oxide is the more enhanced, if 0.5-1 ml

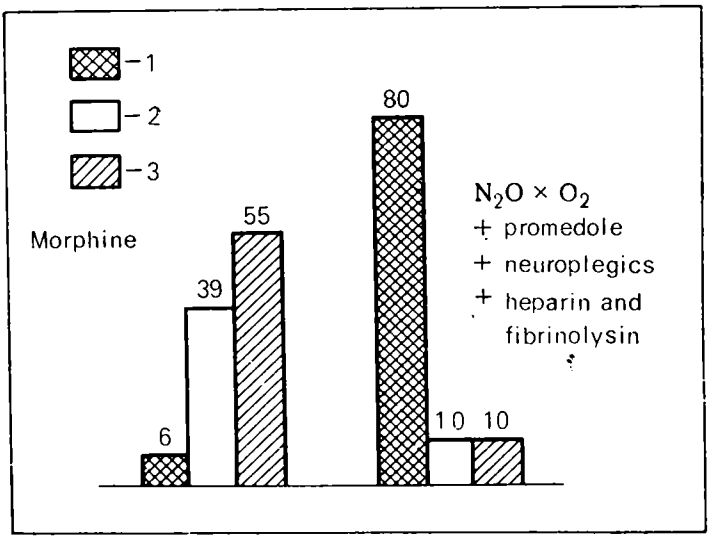

Fig. 72. Effectiveness of various methods of anaesthesia in myocardial infarction

1—total anaesthesia achieved after a single administration of the preparations; *2*—total anaesthesia achieved after several administrations of the preparation and *3*—after their repeated administration

of a 2.5 per cent aminazin solution is simultaneously injected intravenously or intramuscularly.

But any therapy using aminazin has its negative aspects. Aminazin causes a decrease in arterial pressure (both systolic and diastolic), quite substantial in some cases (up to 30 mm Hg) (Hochrein, 1945; Schlicher *et al.*, 1954; and Iosava, 1965). Moreover, tachycardia and, especially, as Petrovsky and Efuni (1967) emphasize, respiratory disturbances may appear. The side effects produced by aminazin, which must be taken into consideration in the therapy of myocardial infarction, limit its use in this disease.

We give much preference in potentiated nitrous oxide anaesthesia to pipolphen (promethazine), which we use very widely in potentiating all the analgesics: pantopon (opium alkaloid), promedol (trimeperidine), analgin (noramidopyrine methanesulphonate), etc.

In its adrenolytic action pipolphen is inferior to aminazin, but is superior to it in its antihistaminic properties. Usually 1-2 ml of a 2.5 per cent pipolphen solution is injected intramuscularly or intravenously. As a strong neuroplegic pipolphen possesses a marked capacity for potentiating the analgesic effect of various narcotics and analgesics. We observed the best results in cases where pipolphen was combined with nitrous oxide. However, a fairly strong analgesic effect can be achieved by combining pipolphen with analgin (40 per cent solution, intramuscularly), pantopon, promedol, etc. (Fig. 72).

It should be emphasized that the foregoing methods of treating the pain syndrome in myocardial infarction are of a symptomatic character and do not exert much influence on the pathological mechanisms which have determined its appearance.

Of considerable interest in this respect are the data on the marked analgesic effect of substances capable of circumscribing and destroying fresh thrombi, i.e. fibrinolytic enzymes and heparin.

Anticoagulative and Fibrinolytic Substances in the Acute Period of Myocardial Infarction

We may discuss the question of the significance of thrombosis in the development of myocardial infarction, its primary or secondary importance, but it goes without saying that formation of a thrombus in the coronary vessels and thromboembolic complications determine not only the severity of this pathological process, but often also its fatal outcome.

Most foreign researchers (White, Wright from USA, Deutsch from Austria, Perlik from GDR, Donaldson from Sweden) and almost all leading Soviet cardiologists (Myasnikov, Lukomsky, Vinogradov, Tareev, and others) deem it necessary to use in myocardial infarction substances which limit thrombogenesis. The recent years were marked not only by the elucidation of a number of mechanisms leading to the development of thrombosis, but also by elaboration of the most rational schemes of treating it. It turned out that the appearance of thrombosis in the coronary vessels is due not only and not so much to an increase in the coagulative properties of the blood, as, in addition to the changes in the vascular wall, to a decrease in the content of natural anticoagulants and depression of the fibrinolytic activity of the blood. An important role is played precisely by the limitation of the capacity for a compensatory increase in the defensive anticoagulative properties of the blood. Hence, the first principle of treating coronary thrombosis is a rapid imitation of the anticoagulation reaction by means of administering heparin and substances enhancing the fibrinolytic activity of the blood (Kudryashov, Chazov, Andreenko, Panchenko, Yanushkevichus). Our observations and the studies of our coworker Nikolaeva have shown that in the acute period of myocardial in-

farction a certain activation of the anticoagulative properties of the blood may be observed. Some pathoanatomists (Vikhert) are inclined even to regard this increase as a cause of the absence of coronary thrombosis in a number of myocardial infarction cases. However, such a reaction is transient and is succeeded by the inhibition of both the anticoagulative and fibrinolytic properties of the blood. According to some observations, the inhibition persists for five to seven days and only after that does the content of anticoagulants and the fibrinolytic activity approach the lower limit of the norm. It is precisely these two pathogenic factors that should be primarily taken into consideration in developing methods of anticoagulation and fibrinolytic therapy in the acute period of myocardial infarction. From this it follows that it is necessary (1) quickly to imitate the natural anticoagulation reaction by administering direct-action anticoagulants and fibrinolytic enzymes, and (2) to take into account the possible depression of the anticoagulative and fibrinolytic properties of the blood on the second or fourth day after the onset of myocardial infarction.

New organizational forms of treating myocardial infarction patients have considerably extended the chances of the physician as regards effective use of substances limiting or lysing the thrombus.

Experimental and numerous clinical findings show that the effectiveness of anticoagulants and fibrinolytic enzymes depends on how soon after the appearance of acute coronary failure the treatment with these substances was begun. The experience of the specialized service confirms the necessity of early administration of heparin and fibrinolytic agents. According to the Leningrad First-Aid Station (Filipchenko *et al.*, 1961), the death rate among patients not treated with anticoagulants amounted to 20.3 per cent, while among patients who received heparin to only 9.6 per cent. Interesting data have been submitted by Kedrov. Mortality among the patients treated with heparin combined with indirect-action anticoagulants was 10.3 per cent, those who received only indirect-action anticoagulants (without heparin) 12.2 per cent and among the control patients not treated with anticoagulants 28.7 per cent. According to Tudhope and Donald (1954), early mortality in myocardial infarction among patients not given anticoagulants reached 40 per cent, but after these substances were introduced into the treatment it decreased to 9 per cent.

Still more important is early therapy with fibrinolytic substances. Numerous experimental studies have demonstrated that an adequate lysing effect is achieved in cases where fibrinolytic enzymes (fibrinolysin, thrombolysin, streptokinase) are used only in the first hours of thrombus existence and when necrotic changes in the myocardium have not set in (Ruegsegger *et al.*, 1960, and Szirmai, 1962). Our coworkers Mazur (1966) and Ruda (1967) specially studied the effectiveness of fibrinolysin and streptokinase depending on the duration of the existence of an experimental thrombus. The

thrombus was produced by administering thrombin and blood serum solution into a temporary isolated portion of the femoral artery. It was possible to destroy the thrombus measuring about 2 cm only when its existence did not exceed four hours.

Clinical findings (Cliffton, 1960; Chazov and Andreenko, 1962; Panchenko, 1962; Yanushkevichus and Bluzhes, 1964; and Gefter, 1967) confirmed the effectiveness of therapy with fibrinolytic enzymes only when they were administered early. This fact, as also the necessity of early heparin treatment, once more demonstrated the expedience of the organizational forms of treating myocardial infarction patients and the main principle of their early admittance to hospital adopted in the USSR. The questions of myocardial infarction therapy with anticoagulants and fibrinolytic enzymes are still debatable in many respects. Although most clinicians hold that for successful treatment of myocardial infarction it is not only justified but also necessary to use anticoagulants in the very first hours of acute coronary failure and to administer heparin in the acute period, there is an opinion that anticoagulants in myocardial infarction are not effective. Still greater controversy arose as to the use of fibrinolytic enzymes. This is due to a considerable degree to the difficulty of evaluating the action of the given substance in myocardial infarction. Much depends on the severity of the process, the patient's age and the adequate use of other substances. Of no smaller importance is the choice of patients in the group being studied and the control group. The studies of Schnur (1954); Russek and Zohman (1954), partly the study of Konyaev (1959) concerned with the use of anticoagulants in myocardial infarction, and the reports of Richter and Imdahl (1962), and Dewar *et al.* (1963) on the use of fibrinolysin not only suggest that the foregoing substances are ineffective in myocardial infarction, but also assert the necessity of the differentiated administration and differentiated evaluation of their action. We consider that in the foregoing studies precisely the last proposition is rational, namely, the necessity of a differentiated approach to the evaluation of their effect. The question of treating myocardial infarction with heparin has been solved by time and by those numerous findings of which Wright *et al.* (1954); Schimert *et al.* (1960); Averina (1962); Shestakov (1962); Straube (1963); Chernov *et al.* (1964); Lukomsky and Kazmina (1967); Chazov (1970), and other authors report.

Heparin in the Acute Period of Myocardial Infarction

Despite the fact that the first reports on the isolation of pure heparin appear as far back as 1918, its wide utilization in the treatment of thromboses began only in the forties. The very first clinical findings showed that heparin possessed marked anticoagulative properties and blocked the system of blood coagulation almost in all its links. These theoretical prerequisites made it possible to raise

the question of using heparin in the treatment not only of thromboses of the peripheral vessels or thromboembolic complications, but also myocardial infarction in which, as is known, most cases involve coronary thrombosis. The expedience of its administration in myocardial infarction was substantiated still more after spasmolytic properties of heparin were discovered. It was found in experiments that heparin dilatates peripheral vessels (Ryazhenov *et al.*, 1963), eliminates coronary spasm caused by pituitrin and leads to an increase in the volume rate of coronary circulation (Gilbert and Nalefski, 1949; and Samoilova and Ryazhenov, 1961).

Some authors (Beligan *et al.*, 1957) noted a decrease in arterial pressure upon administration of heparin in connection with its spasmolytic properties and suggested that in myocardial infarction the substance should be used cautiously, especially in cases of collapse. At the same time, most authors (Civiero *et al.*, 1959; Belkin, 1961; Chazov, 1963; Lukomsky and Kazmina, 1963; Perlik, 1964; Popov, 1964; Khilkevich, 1965, and Smetnev, 1966) did not observe such a decrease in arterial pressure that might affect the course of myocardial infarction. We did not observe deterioration in the condition of even one of the more than 100 myocardial infarction patients in a state of collapse on adding heparin to their treatment.

On the other hand, it is known (Soulier, 1957; Votchal and Magazanik, 1959, and Perlik, 1964) that heparin is an antagonist of serotonin, an increased content of which is one of the factors contributing to the development of shock. That is why administration of heparin may be conducive to prevention of its development.

It is also necessary to point out the third important property of heparin which is connected with its antilipaemic action. Many authors (Ilyinsky, 1952; Myasnikov, 1965, and others) regarded myocardial infarction as an aggravation of atherosclerotic process. By normalizing the disturbed lipid metabolism heparin acts on one of the pathogenic mechanisms of the atherosclerotic process (Myasnikov, Loboda, Leites, Chou-Su, Gero and other authors).

A favourable effect on the course of myocardial infarction is also produced by antagonistic properties of heparin with respect to hyaluronidase which increases the disintegration of hyaluronic acid and is conducive to an increase in the permeability of the vessels. Thus the effect of heparin in myocardial infarction is connected with its action on a number of pathogenic mechanisms.

Fibrinolytic Substances in Myocardial Infarction

To evaluate the action of fibrinolytic substances (fibrinolysin, streptokinase and thrombolysin) in myocardial infarction is much more difficult than that of heparin. Fibrinolytic enzymes began to be used in the treatment of this disease only in the last ten years. The very few observations do not warrant any final conclusions on the true effectiveness and rationality of using them. Our findings

in more than 500 myocardial infarction cases in which fibrinolysin and streptokinase were used show the effectiveness of this therapy. To gain a better insight into the possibilities of fibrinolytic therapy

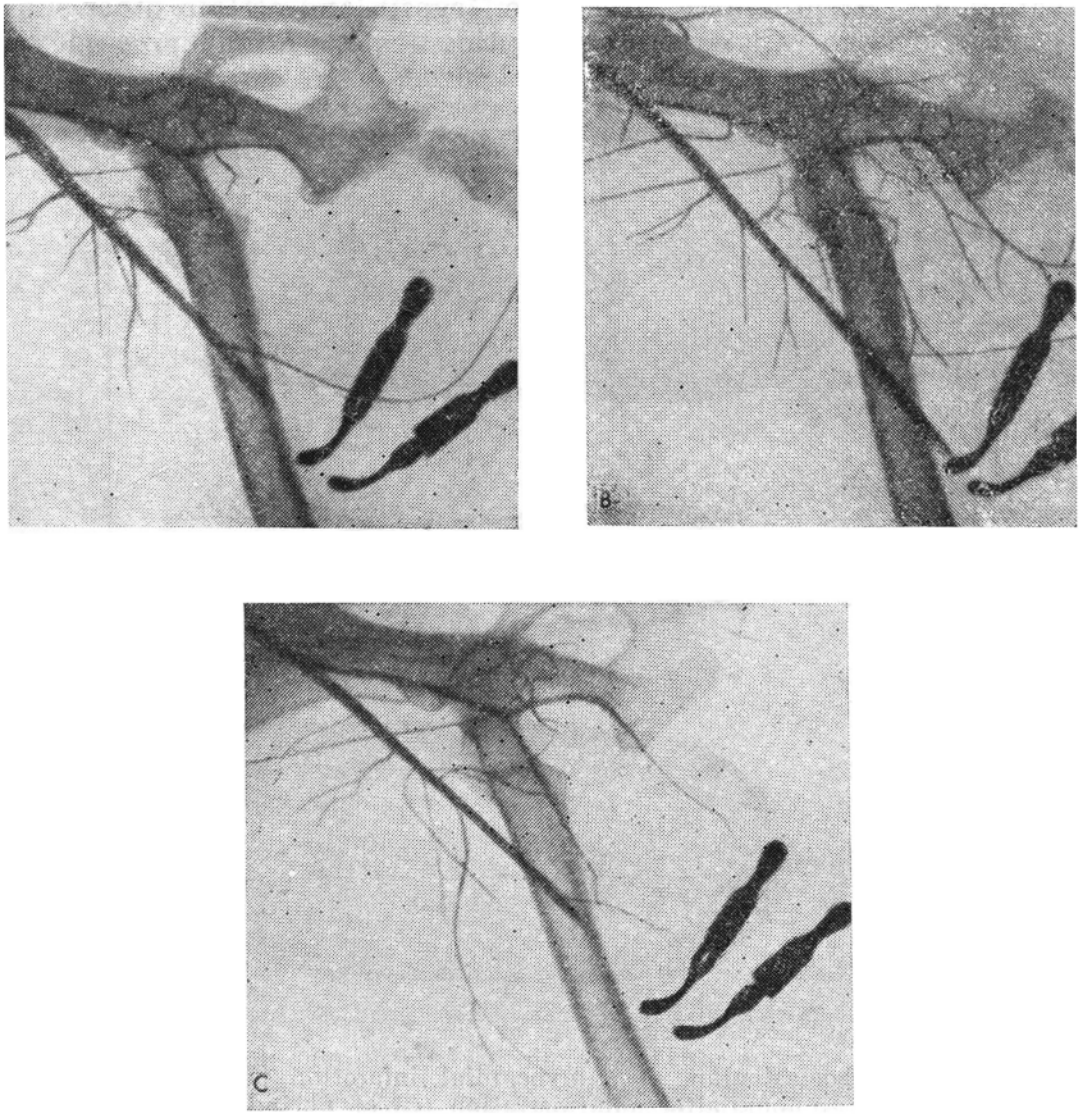

Fig. 73. Lysis of a thrombus of the dog's femoral artery under the influence of fibrinolysin and heparin

A—before beginning of the treatment;
B—two hours after beginning of the treatment
C—recurrent thrombosis ('rethrombosis') 24 hours after final administration of fibrinolysin and heparin (no subsequent administration of heparin)

in myocardial infarction, it is first of all necessary to dwell on certain theoretical principles of using these substances.

As is known, fibrin precipitating as a result of complex coagulation reactions is not an irreversible stage of conversion of proteins and can be destroyed under the influence of fibrinolysin contained in the

blood. Some authors (Astrup, 1963, and Perlik, 1964) have voiced an opinion on the continuous precipitation and disintegration of fibrin. It turned out that fibrinolysin is formed in the blood from an inactive precursor, profibrinolysin, under the influence of various activators, i.e. streptokinase, urokinase, trypsin and certain other substances. The therapy with fibrinolytic substances may proceed by

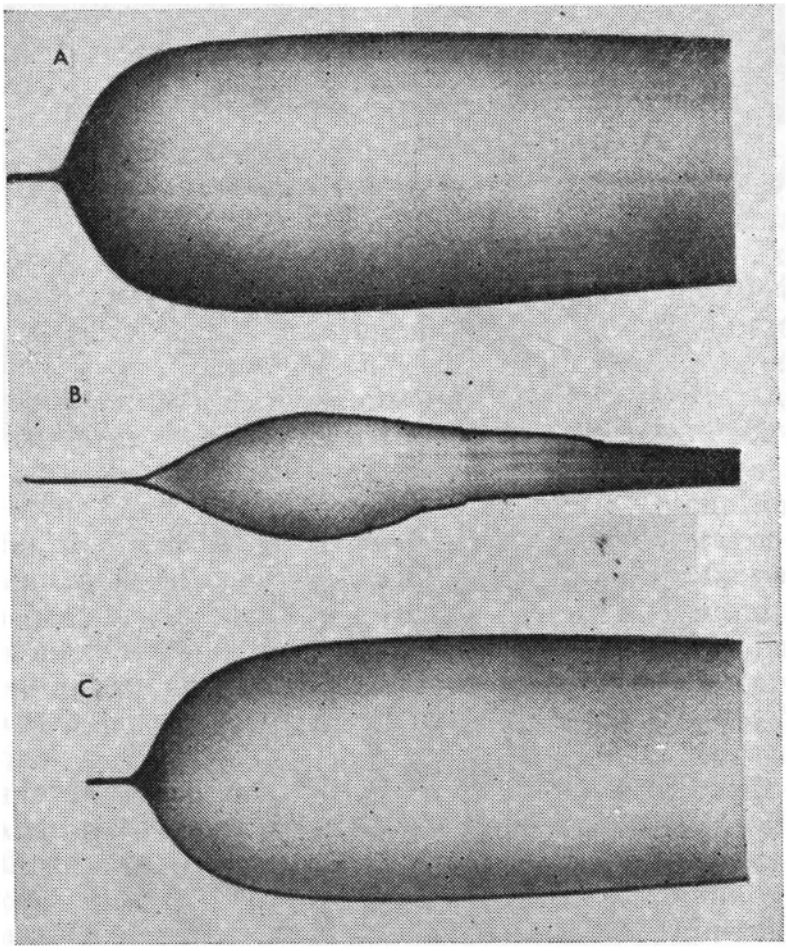

Fig. 74. Thromboelastogram of a myocardial infarction patient before (*A*), during (*B*) and 16 hours after administration (*C*) of fibrinolysin and heparin

way of administering either fibrinolysin activated in vitro from an inactive precursor or its activators (streptokinase, urokinase). According to Coon and Daff (1958), Donaldson (1960) and other authors, the range of fibrinolysin action is wider than mere destruction of fibrin. Moreover, it causes destruction of a number of coagulation factors. In treating myocardial infarction patients with fibrinolytic enzymes it is necessary to proceed from two propositions: (1) the frequency of coronary thrombosis in myocardial infarction, and (2) the fact that in the vessels directly adjacent to the zone of myocardial affection conditions are created due to the local chan-

ges (stasis, inflammatory phenomena, increase in thromboplastic activity) which are conducive to the appearance of what we call the 'secondary' thrombi. They may increase the zone of necrosis and ischaemia produced by 'primary' thrombus and thereby aggravate the severity of the pathological process.

Comparison of the course of myocardial infarction in 500 patients given fibrinolysin and heparin from the very first hours of the disease and that in the control group of patients treated only with

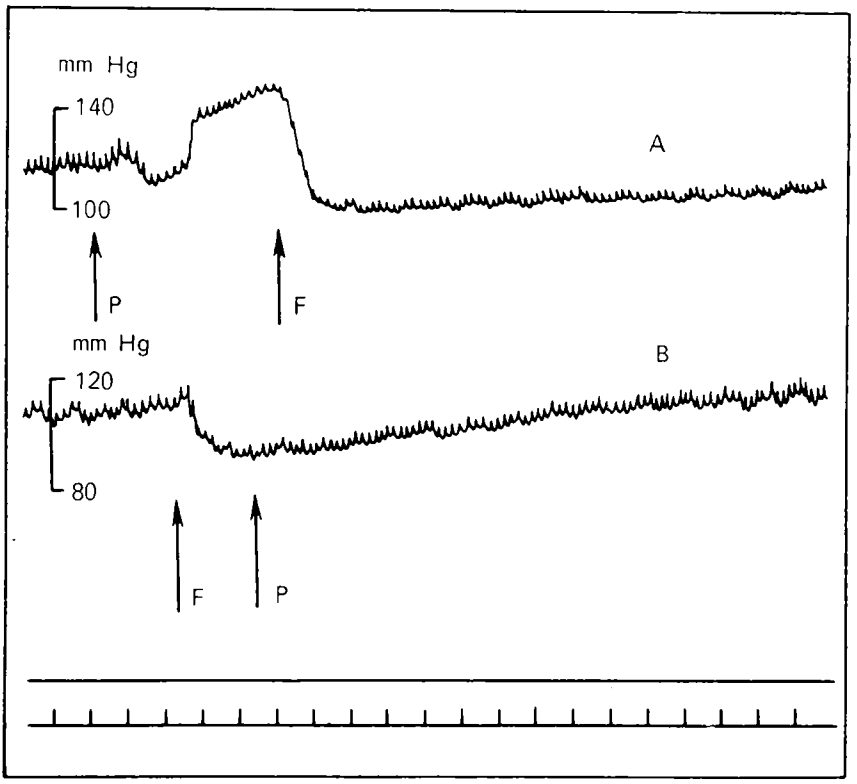

Fig. 75. Changes in the resistogram of the coronary vessels under the influence of administered pituitrin and fibrinolysin

A—elimination of pituitrin spasm with fibrinolysin;
B—prevention of pituitrin spasm by administration of fibrinolysin;
P—administration of pituitrin;
F—administration of fibrinolysin

heparin has shown that the course of the pathological process was much more favourable in cases where fibrinolysin was used (Figs. 73, 74).

A marked analgesic effect of such therapy was also noted by Kozhevnikova and Andreenko (1964), Popov (1964) and Khilkevich (1965). We may argue about the mechanism of analgesic action of fibrinolysin but we hold that it may depend both on the spasmolytic properties of fibrinolysin discovered at our Institute by Mazur and Trubetskoi (Fig. 75), and on the destruction of the 'secondary'

thrombi and connected with this decreased zone of ischaemia and necrosis.

In cases where fibrinolysin was used we observed more rapid dynamics of the ECG, a less marked rise in the level of transaminases, and a normal temperature in 40 per cent of patients (subsequently this was also noted by Yanushkevichus and Bluzhas, 1964; Panchenko, 1964; Popov and Khilkevich, 1965, and Gefter, 1967). In 25 per cent of cases no changes in the blood characteristic of myocardial infarction were found (either leucocytosis was absent or there was no accelerated ESR). The mortality among patients treated with fibrinolysin and heparin was nearly 50 per cent that of the control group. An impression was created that in 10 per cent of cases coronary circulation was either restored or at least compensated, whereas in the other cases the zone of myocardial affection was considerably limited.

It is wrong to think that fibrinolysin therapy can be effective in all cases of myocardial infarction. Its effectiveness depends not only on the time when the treatment was instituted, but also on other factors, namely, the content of profibrinolysin in the clot and concentration of fibrinogen in the plasma, the antifibrinolytic properties of the blood, the content of lipids, the site of administration, etc. As Ruda and Mazur report, fibrinolytic activity increases much less in the arteries than in the vein into which fibrinolysin is administered.

Attendant factors affect the treatment with fibrinolysin activators much less. For this purpose streptokinase is used most extensively. It activates the patient's own profibrinolysin changing it to an active enzyme and possesses a number of peculiarities. On its administration the fibrinolytic blood activity increases rather more slowly, but more markedly than it does on administration of fibrinolysin, and persists on an increased level somewhat longer.

However, the effectiveness of streptokinase in myocardial infarction is close to that of fibrinolysin. Our observations, and those of Mazur, Schnutzler, Van de Leo, and other authors indicate an analgesic effect, rapid dynamics of the ECG, a slight increase in transaminases, and a better prognosis on using streptokinase.

In anticoagulant and fibrinolytic therapy during the acute period of myocardial infarction much depends, in our opinion, not only on how soon it was started, but also in what way and how long these substances were administered. The question of the methods and doses of administration of heparin and fibrinolytic enzymes is still more debatable and complicated than the substantiation for using these substances. Shestakov (1962), a noted Soviet cardiologist, recommends injecting heparin intramuscularly in a dose of 5000 u every four hours during the acute period of myocardial infarction. He sees no advantages in using larger doses because those mentioned above made it possible to achieve the necessary therapeutic level of blood coagulation. On the other hand, Filipchenko *et al.* (1961);

Chernov *et al.* (1964), and Lukomsky and Kazmina (1967), hold that the first doses of heparin should be injected intravenously and the subsequent one intramuscularly.

There is still great controversy on the use of fibrinolytic enzymes; not only the methods of their administration but also the doses are debatable. For example, when fibrinolytic enzymes began to be used, fibrinolysin was usually administered once a day over a period of six or seven hours (Fletcher, Sherry, Datey, Pandya), whereas of late, according to Cliffton, in order to maintain the fibrinolytic activity of the blood on an adequate level the substance is

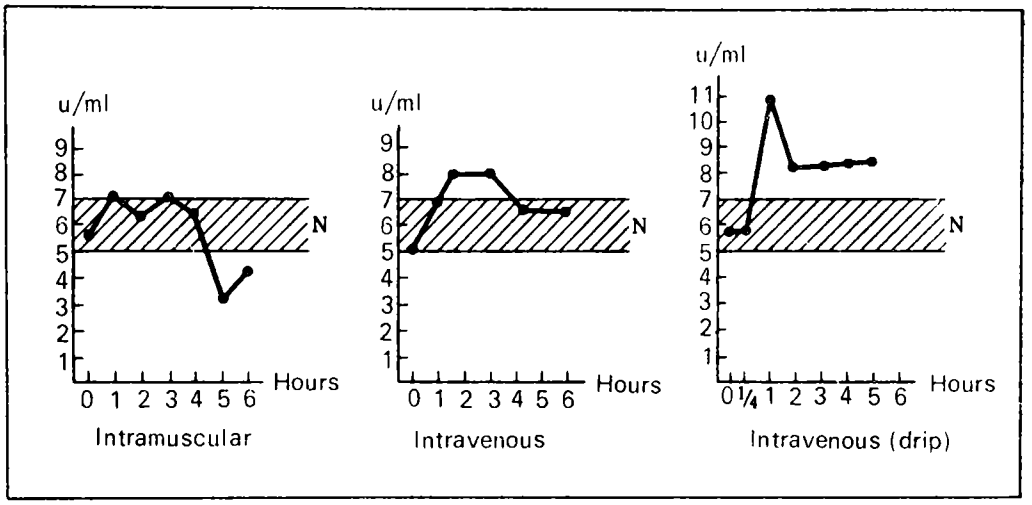

Fig. 76. Fluctuations of the blood heparin level, the substance being administered to man by various methods in a dose of 5000 u.

administered either continuously for one or two days, or twice a day for four or five hours.

The question of the doses of streptokinase is still being discussed. A suggestion is made on the necessity of using larger doses of this substance—up to 1-1.2 million units for a single administration (Donaldson) instead of the usually administered 200 000-400 000 u.

At the Institute of Cardiology we, together with a group of our coworkers (Nikolayeva, Mazur, and Ruda), made a special study of the most effective and rational methods of administering heparin and fibrinolytic enzymes in the treatment of myocardial infarction. To begin with, we have been convinced that intramuscular administration of 5000 u of heparin every 6 hours is absolutely insufficient. As Fig. 76 shows, this method does not ensure a sufficient increase of heparin in the blood and its content usually decreases toward the fifth hour. The adequate increase in its concentration is noted upon intravenous, especially drip administration (see Fig. 76). In these cases during the period between injections the content of heparin in the blood is maintained on a constant high level. Usually

we begin the treatment with intravenous drip administration of 15 000 u of heparin dissolved in 250-300 ml of physiological solution for four or five hours. However, according to the Soviet system of treating myocardial infarction patients, the first-aid physician most commonly begins the treatment with anticoagulants and intravenous stream administration of 10 000-15 000 u of heparin in the patient's home. Subsequently it is necessary to continue heparin treatment by administering not less than 10 000 u intramuscularly or intravenously every five or six hours. Only this dose causes a sufficiently stable increase in the content of heparin in the blood.

There was an opinion that heparin therapy must be continued for two or three days, after which it is necessary to resort to indirect-action anticoagulants (Kushelevsky, 1958; Lukomsky and Kazmina, 1963, and Chernov *et al.*, 1964). But, according to our findings, the treatment must be of a longer duration. This follows from the studies of the dynamics of the endogenous heparin in the blood of 65 myocardial infarction patients carried out from the first hours of the disease by Nikolaeva at the Institute of Cardiology. We think that after certain protective, compensatory increase in the content of heparin in the blood, it decreases beginning from the second or third day of the disease usually to the sixth or seventh day, when it again reaches the normal level. Proceeding from these data we decided to administer heparin therapy in the acute period of myocardial infarction for a longer period. Beginning with intravenous infusion of 15 000 u we administer it intramuscularly or intravenously over three days in a dose of 10 000 u four times a day and intramuscularly during the 4th-5th-6th days in a dose of 20 000 u a day. On the last days of heparin therapy we begin treatment with indirect-action anticoagulants. This scheme of treatment proved more effective than our former practice of 3-day administration of heparin. Of the 50 patients given such prolonged treatment severe attacks of angina pectoris were observed only in one patient, phenomena of circulatory failure in seven and two patients died. It is necessary to emphasize the severe condition of these patients: four of them were admitted with pulmonary oedema, in seven infarction was accompanied with collapse, and 18 exhibited various forms of stable rhythm disturbances.

We consider that in heparin therapy the normal coagulation time must not be increased more than 2.5-fold. The method of thromboelastography is now being more widely introduced into practice. On a background of heparin administration the thromboelastogram undergoes characteristic changes manifested in prolongation of time R, decrease in amplitude K and $m\alpha$. The prothrombin time in heparin therapy may not change although some decrease in the prothrombin index is most commonly observed.

Evaluating various methods we hold that fibrinolytic substances may be administered once a day. Considering that in most cases of myocardial infarction various substances (pressor amines, cardiac

glycosides, polarising mixture, heparin) are administered by the drip method intravenously, it is possible to organize a single prolonged administration of fibrinolytic agents continuing all day. As control over the level of fibrinolytic activity shows, administration of 35 000-40 000 u of fibrinolysin or 300 000-350 000 u of streptokinase over four or five hours under condition of an adequate heparin therapy ensures a stable increase in the fibrinolytic activity of the blood.

The findings of recent years make it possible to recommend higher doses of fibrinolysin in treating myocardial infarction than those we recommended before (Chazov, 1963, 1966).

By comparing the results of fibrinolysin administration in three groups of myocardial infarction patients (in dosages of 25 000-30 000, 35 000-40 000 and 50 000-60 000 u) we found the dosage of 35 000-40 000 u to be most expedient. In cases with larger doses (50 000-60 000 u) side effects (fever, chills, sometimes dyspeptic phenomena) developed in nearly 50 per cent of cases. Haemorrhagic phenomena were noted in three patients on a background of a marked and stable increase in fibrinolysin. In a group of patients given 35 000-40 000 u of fibrinolysin in the absence of marked side effects the results (concerning the analgesic action, influence on the ECG dynamics, extent of the focus of affection, complications) were more favourable than in patients given fibrinolysin in a dose of 25 000-30 000 u. Similarly the most effective and safe were the doses of streptokinase (300 000-350 000 u).

In evaluating the action of fibrinolytic enzymes we proceed from the indices of fibrinolytic activity of the blood and thromboelastography. There are various methods of determining the fibrinolytic activity of the blood, those of Bidwell (Andreenko and Chazov, 1964), of Kaulla and Schultz, and of Kavalsky must be considered the most widespread. All these methods are based on the study of the lysis of the standard fibrin clot under the influence of fibrinolysin of the blood.

The data furnished by thromboelastography are very demonstrative. An increase in fibrinolytic activity of the blood is marked by a characteristic decrease in the *ma* amplitude and in a number of cases by its complete disappearance.

It goes without saying that many questions of therapy with fibrinolytic substances and heparin are still debatable, since much remains unstudied, however, it may be stated already today that wide introduction of all the foregoing substances into the practice of treating myocardial infaction considerably improves its prognosis.

Treatment of Shock

The organization of specialized first-aid teams and early admittance of myocardial infarction patients into hospitals resulted in the fact that the patients are under active medical observation from

the very first hours of the disease. This period of the disease, and especially the complications which arise in the first hours of infarction, have attracted considerable attention.

This applies, in the first place, to the treatment of shock (collapse)[1]. As the observations of various authors show the prognosis in collapse largely depends on the period of time that has elapsed from the moment of the appearance of this complication to the beginning of the treatment. A. V. Vinogradov (1965) reported that in collapse lasting more than four hours the mortality was four times as high as in the same, but more transient, complication. When the therapy is begun during the first hour, a favourable result is observed in 75 per cent of cases, whereas, when it is started later than 12 hours, all the patients die. According to Smetnev and Belkin, in cases of collapse lasting five to ten hours mortality amounts to 85-90 per cent. If, however, active therapy begins sooner than three hours after the apperance of this complication, mortality is decreased to 30 per cent. Tochowicz and Pasyk (1965) noted that among the patients in whom treatment was begun later than in one hour the mortality amounted to 82.5 per cent.

Of course, in evaluating the effectiveness of the therapeutic measures it is necessary to consider the severity of the collapse.

Having analysed together with Smetnev and Ruda the effectiveness of treating more than 500 patients with collapse (this material was reported to the All-Union Conference on Cardiogenic Shock in 1969) we were able to distinguish four groups of patients, four forms of this complication of acute myocardial infarction. This division is based on the clinical picture of the disease and the peculiarities of the reaction to the treatment.

In our opinion, the first form is vascular failure proper which accompanies the appearance of myocardial infarction. It is the form that can be relatively quickly terminated by administration of mesaton (phenyliphrine), cordiamine (nikethamide) or other vascular agents. Its treatment is usually administered and finished in the stage of first and urgent aid. This form occurs often, approximately in 35 per cent of cases of cardiogenic shock. In time, if the appropriate therapy was begun late, this form may develop into the so-called areactive form. This is due to the increase in acidosis, disturbance in microcirculation and in the function of certain endocrine system.

The second form has considerable pathogenic peculiarities and is therefore an entity of its own. We associate its appearance with severe disturbances in rhythm and conduction. As observations involving continuous automatic control of the ECG show, it occurs in about 5 per cent of shock cases. The treatment of this form must

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[1] The term 'collapse' is used as an equivalent of the term 'cardiogenic shock' since it is quite widespread in Soviet literature. However, it does not reflect the essence of the changes in this complication of myocardial infarction.

begin with restoration of the rhythm (electro-impulse therapy, antiarrhythmic agents—novocainamide [procainamide], lidocain, [lignocaine, DDA], giluritmal [ajmaline], etc.) or normalization of conduction (steroid hormones, isuprel [isoprenaline], hypothiazid [hydrochlorothiazide]). In these cases it is enough to restore the rhythm for the signs of acute circulatory failure to disappear.

The third form is characterized by considerable disturbances in contractility of the myocardium, which is often combined with an inadequate compensatory reaction of the peripheral vascular bed to the decrease in the minute volume of the heart. The mechanism of the appearance of all cases of collapse has until recently been considered from these positions. Today we can distinguish a certain group of patients in whom the mechanism appears in the 'pure' form, and the best results are achieved by combined administration of cardiac glycosides and pressor agents.

The fourth form, in our opinion, comes closest to shock in its usual conception. An important role in its appearance is played by the development of acidosis, disturbed microcirculation, thrombosis of arterioles and capillaries, decreased venous inflow to the heart, and hormonal changes (Fig. 77). These are most commonly the so-called areactive cases in which therapy proves ineffective. In these cases analgesics, cardiac glycosides, steroid hormones, α-adrenal blocking agents, low molecular dextran, fibrinolysin or streptokinase are used with simultaneous administration of heparin.

Speed and efficiency in administering the appropriate substances constitute one of the most important conditions of successful treatment of collapse. Not all the mechanisms of the appearance of collapse are as yet known; nor are there any universal methods of treatment. By taking some haemodynamic, metabolic and hormonal peculiarities of various cases of shock into account one can draw a conclusion that there are no universal agents. We must concur with a number of authors (Kuhn, 1967; Lukomsky *et al.*, 1967, and others) that the group of myocardial infarctions with a clinical picture of shock embraces the cases which are heterogeneous from the pathogenic point of view. In such patients there may be, for example, different haemodynamic changes. In treating shock today we cannot and do not in most cases take all these peculiarities into consideration. In fact, if we were in a position quickly and accurately to evaluate the state of peripheral resistance and its relation to the contractility of the myocardium, if we could accurately evaluate the extent of the venous inflow to the heart and the peculiarities of regional blood supply, the measures taken in collapse would be strictly individualized and more effective.

Is it always necessary to strive for an increase in peripheral resistance during shock or combine the use of vasoconstrictive and vasodilatative substances? Is it always expedient to use substances influencing the contractility of the myocardium? Can the method

of auxiliary circulation facilitate the task of physicians at the bedside of the patient with collapse? These are but few of the unsolved problems on which administration of pathogenically substantiated treatment of collapse depends.

Modern methods of treatment are largely symptomatic. Considering the main signs of collapse, namely, marked decrease in contractility of the myocardium and hypotension, the first to be ad-

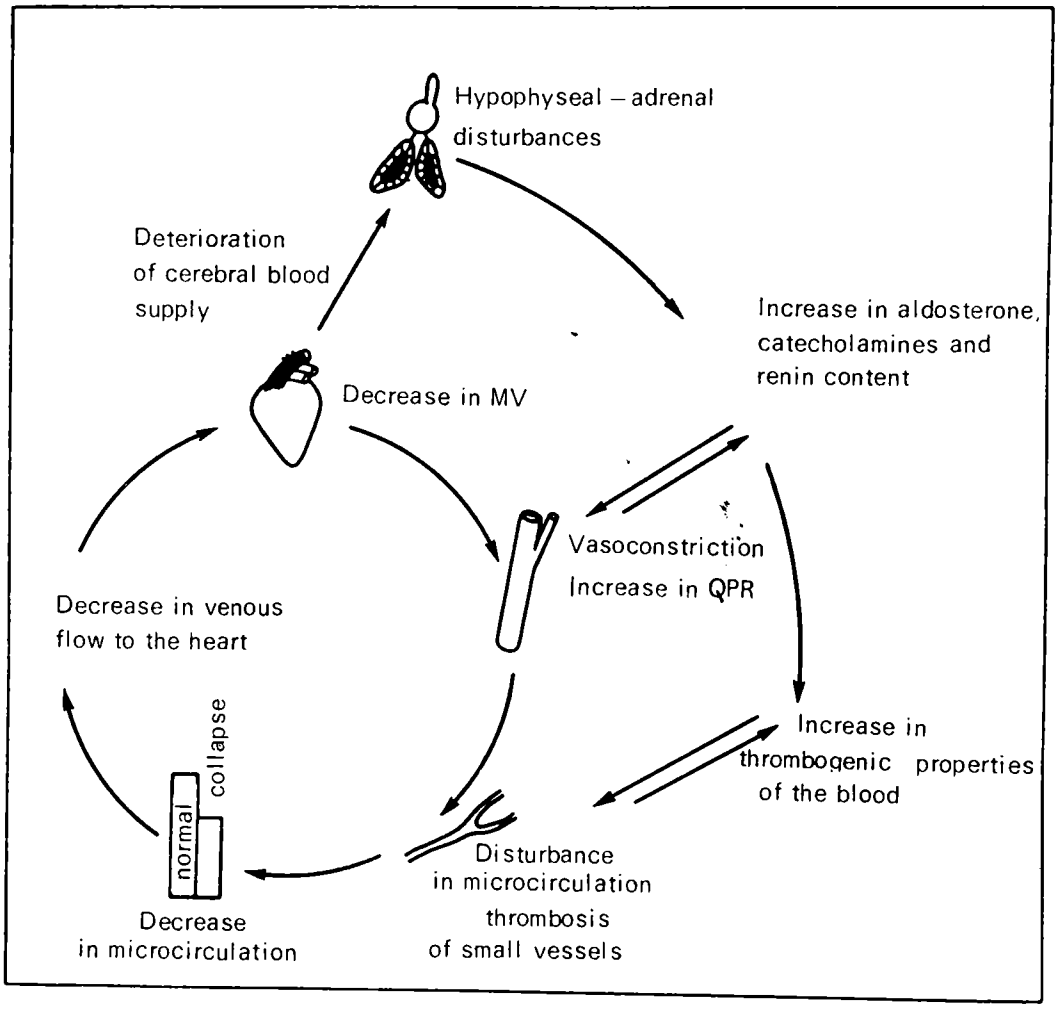
Hypophyseal – adrenal disturbances
Deterioration of cerebral blood supply
Increase in aldosterone, catecholamines and renin content
Decrease in MV
Vasoconstriction
Increase in QPR
Decrease in venous flow to the heart
Increase in thrombogenic properties of the blood
normal
collapse
Disturbance in microcirculation thrombosis of small vessels
Decrease in microcirculation

Fig. 77. Diagram of the pathogenesis of cardiogenic shock

ministered are substances whose point of application are the mechanisms which account for the maintenance of arterial pressure and an improvement in the contractility of the myocardium.

The opinion voiced by some authors (Eckenhoff *et al.*, 1947, and Kogan, 1958) that hypotension that arises in myocardial infarction favourably affects the heart by decreasing its work and thereby being a protective unloading reflex, as it were, was discarded by life itself when wide introduction of vasopressor substances made it

possible considerably to improve the prognosis in collapse. On the other hand, clinical and experimental findings (Cordey *et al.*, 1949; Vinogradov, 1965; Smetnev, 1966) not only elucidated the role of myocardial insufficiency in the development of hypotension, but also demonstrated the significance of the decrease in the arterial pressure for the disturbances in contractility of the myocardium.

That is why administration of substances increasing arterial pressure in collapse seems to be expedient. This applies, in the first place, to the first form and to a lesser extent to the third form described by us.

It is known that a considerable number of cases of myocardial infarction is accompanied, in addition to a decrease in contractility of the heart muscle, with a compensatory increase in peripheral resistance. Studies of recent years make it possible to evaluate with greater differentiation the state of vascular tone in the various parts of the vascular system. In collapse, in addition to marked spasm of renal vessels, for example, dilatation of the vessels of the skeletal muscles is observed. Thus, general peripheral resistance being a summary resistance of the various parts of the vascular system, may not completely reflect the fine changes which occur on the periphery. It is considered that an increase in peripheral resistance during collapse is not enough to prevent a decrease in arterial pressure. Hence it is clear why attempts are made to increase the tone of the peripheral vessels in order to achieve disappearance of the signs of collapse.

Of the medicinal substances which increase vascular tone a Soviet preparation mesaton (phenylephrine) is most extensively used. Its introduction into the treatment of collapse marked a new stage in the therapy of this severe complication of myocardial infarction. Administration of mesaton has not only made it possible successfully to control relatively mild shock, but has also given the physicians a substance which enables them in some measure to evaluate the severity of this complication. Mild cases of collapse are characterized by a rapid and stable reaction to intravenous or intramuscular administration of 1 ml of 1 per cent mesaton solution (in intramuscular administration the reaction appeares in ten minutes, in intravenous administration during the very first minute).

Mesaton, original Soviet vasopressor, was synthesized in the fifties. However, its wide application began in 1959-1960 after A. V. Vinogradov's studies which revealed its great effectiveness and especially after specialized aid to infarction patients was organized.

Mesaton closely resembles adrenalin, but, differing in chemical structure only by the absence of one hydroxyl group, it differs very much in action. It possesses more pronounced vascular action and exerts much less influence on the heart (Votchal, 1963). It produces a lesser pressor effect than does adrenalin, but this effect persists much longer. If we consider that mesaton dilatates the coronary arteries and is capable, although not to a very great extent, of in-

creasing the power of cardiac contractions the rationality of its administration to myocardial infarction patients in shock becomes comprehensible.

Mesaton is administered intramuscularly in a dose of 0.5-1 ml of a 1 per cent solution. It may also be given by the drip method intravenously in physiological solution or in a 5 per cent glucose solution in doses of 30-40 mg per 500 ml of the solution. The initial rate of mesaton administration by the drip method is 20-30 drops per minute.

Mesaton proved very effective mainly in relatively mild cases of shock. According to A. V. Vinogradov, the pressor reaction was observed in 86.1 per cent of cases. The good pressor effect of mesaton is also reported by other authors (V. N. Vinogradov *et al.*, 1957; Lukomsky, 1964; Moiseev, 1965, and others). In recent years (1964-1965) we noted a somewhat lesser effectiveness of mesaton in collapse, i.e. a positive pressor reaction was observed only in 62.5 per cent of cases. In studying a contingent of patients hospitalized in 1961-1963 and in 1964-1966 we found an inerease in the number of patients with severe forms of myocardial infarctions, extensive affections of the heart and severe collapse which hardly yielded to therapy with pressor amines. This emphasizes once more the complexity of evaluating the therapeutic measures taken in myocardial infarction where much depends on the contingent of patients.

In severe cases of collapse (the third form) the therapeutic effect is achieved not only by administration of more active vasopressors —noradrenalin, hypertensin (angiotensin), but also by introduction into the combined therapy of rapid-action cardiac glycosides—strophanthin and corglycon. This confirms the opinion that in the development of severe forms of collapse during myocardial infarction an important role is played by a decrease in the contractility of the myocardium.

In cases when the administration of mesaton alone or in combination with cardiac glycosides does not produce any effect, noradrenalin is usually resorted to. It belongs to the group of sympathomimetic amines and is a mediator of the sympathetic nervous system. It possesses marked pressor action which exceeds that of adrenalin and is due to a more pronounced narrowing of the peripheral vessels, especially the vessels of the muscles (Sabelli, 1961; Pisha and Gamer, 1963; Votchal, 1963; Luisada and Rosa, 1965; V. N. Vinogradov *et al.*, 1965). Zakusov (1953) associates the vasoconstrictive action of the substance with its direct influence on the neuromuscular structures of the vessels. In addition to this noradrenalin increases the oxygen requirement of the myocardium much less than adrenalin, which is particularly important in myocardial infarction where this increase may not only aggravate the severity of the pathological process, but may also be conducive to the appearance of new foci of ischaemia.

Experimental findings (Garb, 1950, and Lu and Melville, 1951)

showed the capacity of noradrenalin to increase the strength of cardiac contractions, which is particularly important under conditions of its decrease in myocardial infarction. The data on the influence of noradrenalin on the coronary circulation are less definite. Some authors report an increase in coronary circulation on administration of sympathomimetic amines (Winbury and Green, 1952; Frank *et al.*, 1956). This stands to reason, because an increase in pressure in the aorta is conducive to an increase in coronary circulation. At the same time the experiments conducted by Novikova at the Institute of Cardiology using the most accurate bubble method of studying coronary circulation did not produce any convincing data on the coronary dilatative properties of noradrenalin and its capacity to increase coronary circulation.

It should be emphasized that noradrenalin does not cause tachycardia. It is administered only by the drip method. We usually dilute 1-2 ml of a 1 per cent noradrenalin solution in 350 ml of physiological solution and administer it intravenously at the rate of 10-40 drops per minute.

Administration of noradrenalin requires thorough watching of the level of arterial pressure because the dose of the substance (the rate of administration of the solution) depends on the reaction, level and stability. Careful watching of the level of arterial pressure is also important because signs of collapse may disappear before the organism's capacity independently to maintain the arterial pressure at a normal level has been restored. A negative property of noradrenalin is the possibility of the appearance of necroses at the site of its administration and the development of phlebitides during its prolonged administration. Even thromboses of the veins upon prolonged administration of noradrenalin have been described. These side effects limit the duration of noradrenalin administration.

According to most authors (Miller and Baker, 1952; Myasnikov, 1965; A. V. Vinogradov, 1965 and V. N. Vinogradov *et al.*, 1965), treatment with sympathomimetic amines considerably improved the prognosis in collapse connected with myocardial infarction and decreased the mortality in this complication almost 50 per cent.

During the long observation of patients with myocardial infarction aggravated by collapse we were convinced that the effectiveness of sympathomimetic amines in cases of mild collapse and in severe forms of this complication is different. For example of the 56 patients with a mild form of shock sympathomimetic amines (without additional administration of other medicinal substances) proved effective in 45; in four cases combined therapy was necessary, including cardiac glycosides and corticosteroids, and seven patients died.

At the same time treatment with sympathomimetic amines was administered to 19 patients with severe collapse; 16 of them died. These figures show that sympathomimetic amines are more effective

in cases of relatively mild collapse when vascular failure comes to the fore.

In severe, so-called areactive, form of collapse not only the pressor effect of vascopressor substances is absent, but in a number of cases a further decrease in arterial pressure is observed. We did not observe a positive effect produced by these substances even in one of the 147 cases of 'areactive' collapse (Chazov and Smetnev, 1969). Noradrenalin sometimes aggravates pulmonary oedema which often accompanies cardiogenic shock. Moreover, in cases of the 'areactive' form of shock a progressive decrease in arterial pressure was observed despite the increase in the mean dose of noradrenalin to 7.7 mg.

The opinion that pressor amines can solve only the problem of relatively mild forms is supported by a number of authors. Even the great advocates of the use of pressor amines V. N. Vinogradov and Smetnev report nearly 100 per cent mortality in third degree collapses (V. N. Vinogradov's classification). According to Smetnev (1969), of the 124 patients with third degree collapse treated with noradrenalin and mesaton 119 died; Cronin *et al.* (1965) report their observations of two groups of patients with cardiogenic shock; 17 per cent of the patients treated with noradrenalin and 18 per cent of the patients not treated with pressor amines survived.

This explains the continuous quest for new methods of treating collapse. In this connection of some interest are the attempts at using angiotensin (hypertensin). As is known, angiotensin is a polypeptide and an active pressor which forms under the action of renin on plasma angiotensinogen. Dispenced under the name of 'hypertensin' it produces a more strongly pronounced pressor effect than does noradrenalin.

The rationality of using angiotensin is confirmed by the studies of the state of certain enzymes in myocardial infarction. As Zysko and Serebrovskaya (1969) show, in myocardial infarction the content of renin in the blood gradually increases from the very first day. It may be assumed that it is a compensatory increase and that the acute period of the disease is characterized by its relative deficiency and, consequently, insufficient formation of angiotensin.

Two substances are now distinguished: α- and β- angiotensin II (hypertensin); according to the reports of some authors, the β-substance proved more active in both experimental and clinical observations. According to Imhof *et al.* (1964) on administration of 100 γ of the α-substance the arterial pressure increased only in 35 per cent of patients with shock, while on administration of the β-substance in 85 per cent.

We usually use angiotensin II in a dilution of 2.5-5 mg per 350-400 ml of physiological solution. Angiotensin is administered at the rate of a few and up to 20-40 and more drops per minute, depending on the level and reaction of arterial pressure. It is necessary to remember that an overdose of the substance causes a hypertensive

reaction resembling the hypertensive crisis (tachycardia, headache and mild tremor). At the same time angiotension is devoid of a number of side effects characteristic of noradrenalin. It is particularly important that inflammatory changes do not develop in the vein into which the substance is infused, for which reason it may be administered for a long time without interruption. Zysko, who studied the action of hypertensin at the Institute of Cardiology, reports cases of its continuous administration even over a period of three days. Cessation of hypertensin administration immediately resulted in a decrease in arterial pressure, and the appearance of marked signs of shock which disappeared only upon resumption of the treatment. This confirms the opinion of many specialists that an increase in arterial pressure does not as yet mean elimination of shock (Agress and Binder, 1957; A. V. Vinogradov, 1965, and other authors). Only disappearance of all clinical manifestations of this complication indicates a positive effect of the treatment.

The observations carried out at the Institute of Cardiology have demonstrated greater effectiveness of hypertensin treatment compared with that of noradrenalin. Thus, of the 17 patients with severe collapse in whom only a temporary unstable pressor effect was observed on administration of noradrenalin, the signs of shock disappeared completely in 12 after the treatment with hypertensin. It is interesting to note that, although the pressure increased in five patients almost to normal figures (90/60-115/90 mm Hg) on a background of hypertensin treatment, their condition did not improve and all of them died. In 14 patients administration of hypertensin failed to cause any reaction (Fig. 78).

While extending the possibilities of treating collapse, hypertensin at the same time cannot radically solve the problem of treating this severest complication of myocardial infarction.

Reports, in which considerable importance was attached to hypertensin as a substance capable of changing the prognosis for patients with severe forms of collapse, were followed by other ones in which hypertensin was regarded solely as one of the substances in the complex of agents for controlling this complication. In some studies the effectiveness of hypertensin was generally doubted. According to Beanlands and Cunton (1964), in particular, the mortality among patients given angiotensin was 82 per cent, whereas among those given noradrenalin 78 per cent. Some authors (Fowler and Holmes, 1964) point out the properties of the substance which may negatively affect the course of myocardial infarction. Angiotensin, in particular, may cause a decrease in cardiac output. One of the editorials of the *British Medical Journal* (1966, 2, 5512, 481-483) mentions a possibility of coronary spasm during treatment with angiotensin. It should be pointed out that in none of the cases did we observe any signs indicating deterioration of coronary circulation during hypertensin treatment.

As we have already pointed out, an important role in the patho-

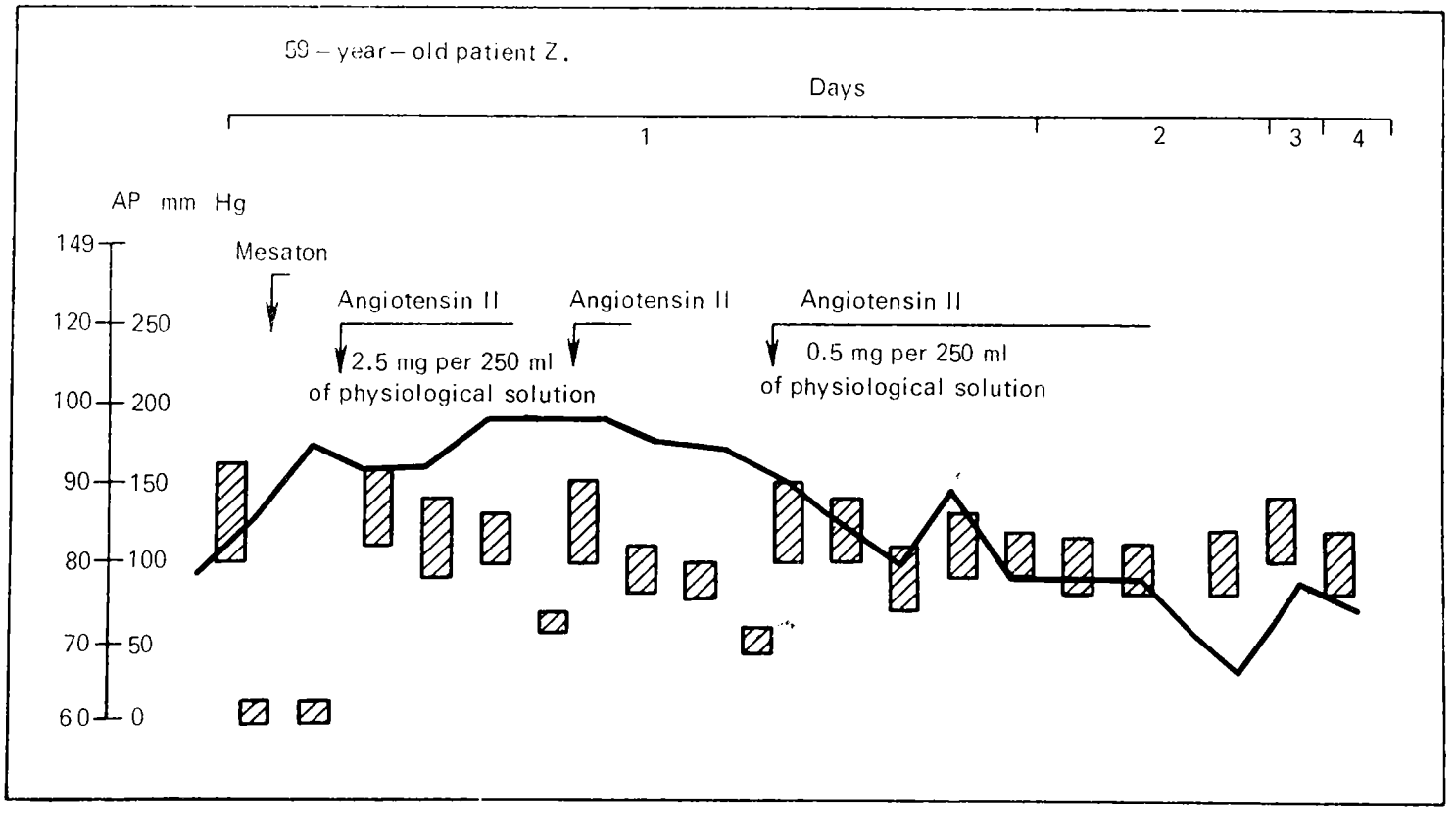

Fig. 78. Changes in arterial pressure with cardiogenic shock under the influence of intravenous drip administration of hypertensin

genesis of collapse is played by a decrease in myocardial contractility accompanied with a decrease in the minute volume. The wide use of cardiac glycosides in its treatment is therefore comprehensible and justified. Despite the fact that suggestions to use strophanthin in collapse, as a quickly acting substance devoid of many side effects, were known long ago (a suggestion to make more extensive use of strophanthin in myocardial infarction may be found in Gelschtein's monograph which notes its high effectiveness) it began to be used more or less widely only of late. But even today many physicians prescribe it with caution.

We use strophanthin in combination with noradrenalin or hypertensin in all cases where the primary administration of mesaton is either ineffective or it produces a transient and unstable increase in arterial pressure.

The necessity of administering cardiac glycosides in collapse is recognized by most Soviet clinicians who have noted a better prognosis in cases where strophanthin or corglycon is administered simultaneously with pressor amines (Shestakov, 1962; Lukomsky, 1963; A. V. Vinogradov, 1965; V. N. Vinogradov *et al.*, 1965). According to Smetnev *et al.* (1965) of 544 myocardial infarction patients strophanthin or corglycon was administered to 384. Foreign literature contains increasingly more reports on the favourable action of cardiac glycosides in collapse. Moreover some authors (Cronin, 1967) hold that the problem of cardiogenic shock will be solved not with vasopressor substances, but precisely with cardiac glycosides.

Strophanthin is usually given intravenously in a dose of 0.25-0.5 mg (0.5-1 ml of 0.05 per cent solution) in 20 ml of 40 per cent glucose or physiological solution. We observed a better effect when strophanthin or corglycon was administered by the drip method (1 ml). The doses of the aforesaid substances were put in an installator through which pressor amines or hypertensin diluted in 300-350 ml of physiological solution or a 5 per cent glucose solution were administered. We must emphasize the necessity for thorough electrocardiographic control (preferably with the use of the monitor system) when administering cardiac glycosides in cases of myocardial infarction, especially when it is complicated by collapse. Uncontrolled administration may lead to the appearance of glycoside intoxication and severe disturbances in rhythm (Fig. 79).

We regard marked bradycardia (with a heart rate of less than 60 per minute) and disturbances in conduction as contra-indications for cardiac glycosides. However, the use of cardiac glycosides, while extending our therapeutic potentialities and improving the prognosis in a number of cases of shock during myocardial infarction, has not completely solved the problem of controlling especially the severe, 'areactive', forms of this complication.

This is largely due to the fact that the mechanisms of collapse do not merely consist in a decrease in myocardial contractility and haemodynamic disturbances. Myocardial infarction complicated by

collapse is a peculiar stress which leads not only to changes in the heart and even the organs of circulation, but also to a disturbance in the functions of other systems, the endocrine system in particular. One gathers the impression that it is characterized by exhaustion of all the defensive mechanisms (those regulating circulation, the anticoagulation system, and finally the appearance of relative adrenal insufficiency, etc.).

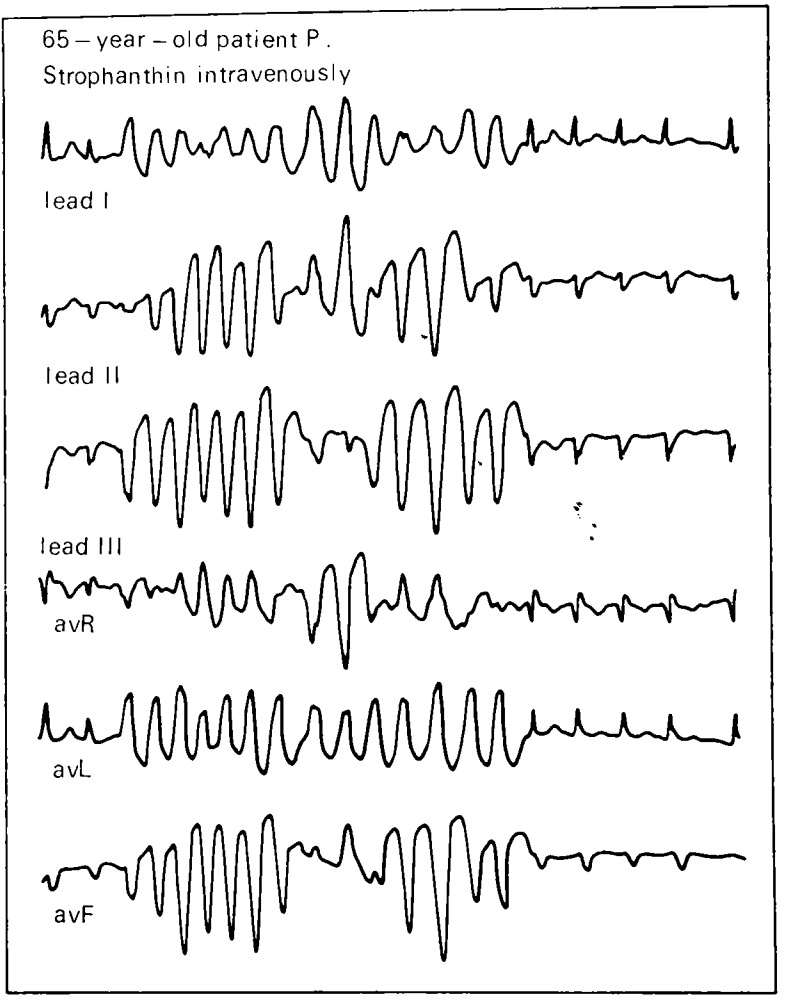

Fig. 79. Disturbances in cardiac rhythm provoked in myocardial infarction patient by intravenous administration of 0.5 mg of strophanthin

This is why more and more authors incline to the necessity of combined treatment of shock. In addition to vasopressor substances and cardiac glycosides they suggest administration of corticosteroids. The question of using steroid hormones is also being discussed. Although some authors (Vinogradsky, Usvatova, Smetnev) have observed greater effectiveness of combined therapy including cortisone, hydrocortisone and prednisolone the problem of using these substances still requires further investigation.

Smetnev, for example, used in 42 cases of second degree collapse (according to V. N. Vinogradov's classification) hydrocortisone combined with pressor amines and cardiac glycosides in a single dose of 25-50 mg and in 30-60 minutes noted a stable positive reaction in all cases, except one. The total dose of the preparation varied between 50 and 550 mg. According to the Kiev First-Aid Station (Zilberman, 1967), inclusion of corticosteroids (100-125 mg hydrocortisone, 30-40 mg prednisolone) in the treatment of collapse made it possible to reduce mortality among these patients from 50 to 38 per cent. Administration of hydrocortisone, however, did not change essentially the prognosis for patients with severe collapse.

We have had the impression that corticosteroids, while favourably influencing the course of mild collapse, are ineffective in its so-called areactive form.

What, then, are the immediate prospects for elaborating new methods of treating shock in myocardial infarction? In discussing this problem we cannot help but dwell upon the question of the effectiveness and expedience of administering vasodilators in collapse. Eichna (1967); Gabor (1967); Dietzman and Lillehei (1968), and other authors hold that compensatory vasoconstriction which appears in collapse may negatively affect the course of the disease if it persists for a long time. Vasoconstriction fosters compensation for the decrease in the minute volume of the heart, but, in the opinion of the foregoing authors, subsequently not only increases the load on the heart, but also deteriorates the perfusion of the tissues, which leads to the development of hypoxia and metabolic acidosis.

On the basis of the aforesaid we can recommend for the treatment of collapse combined therapy with blocking agents of α-adrenergic receptors (phenoxybenzamine) and simultaneous administration of low molecular dextran. Shestakov (1962); Bloch *et al.* (1965); Cronin (1967); Eichna (1967); Gabor (1967), and Dietzman and Lillehey (1968) report successful administration of chlorpromazine (aminazine) for sympatholytic therapy.

In 21 cases of severe collapse we administered jointly with Smetnev thalamonal, a substance which contains dehydrobenzperidol, a blocking agent of the α-adrenergic receptors. The substance was used on a background of low arterial pressure which we were unable to correct by the administration of cardiac glycosides and pressor amines. Administration of thalamonal to 15 patients on this background resulted in a gradual increase in arterial pressure and disappearance of the peripheral signs of collapse. The administration of thalamonal was combined with that of low molecular dextran (Fig. 80).

Experimental and clinical studies in the use of substances stimulating the β-adrenergic receptors in collapse have of late been carried out in other countries. We observed 12 cases in which one of these preparations, isuprel (isoprenaline), was used; however, we cannot see any advantage in this method of treatment.

We attach considerable importance to the use of auxiliary circulation, the counterpulsation method in particular. The essence of the method is that simultaneously with the patient's heart we operate a pump connected with it, which takes upon itself some part of the propulsive work of the heart. It is assumed that during this period the heart will recover its working capacity to such an extent that it will subsequently be able to ensure adequate circulation by

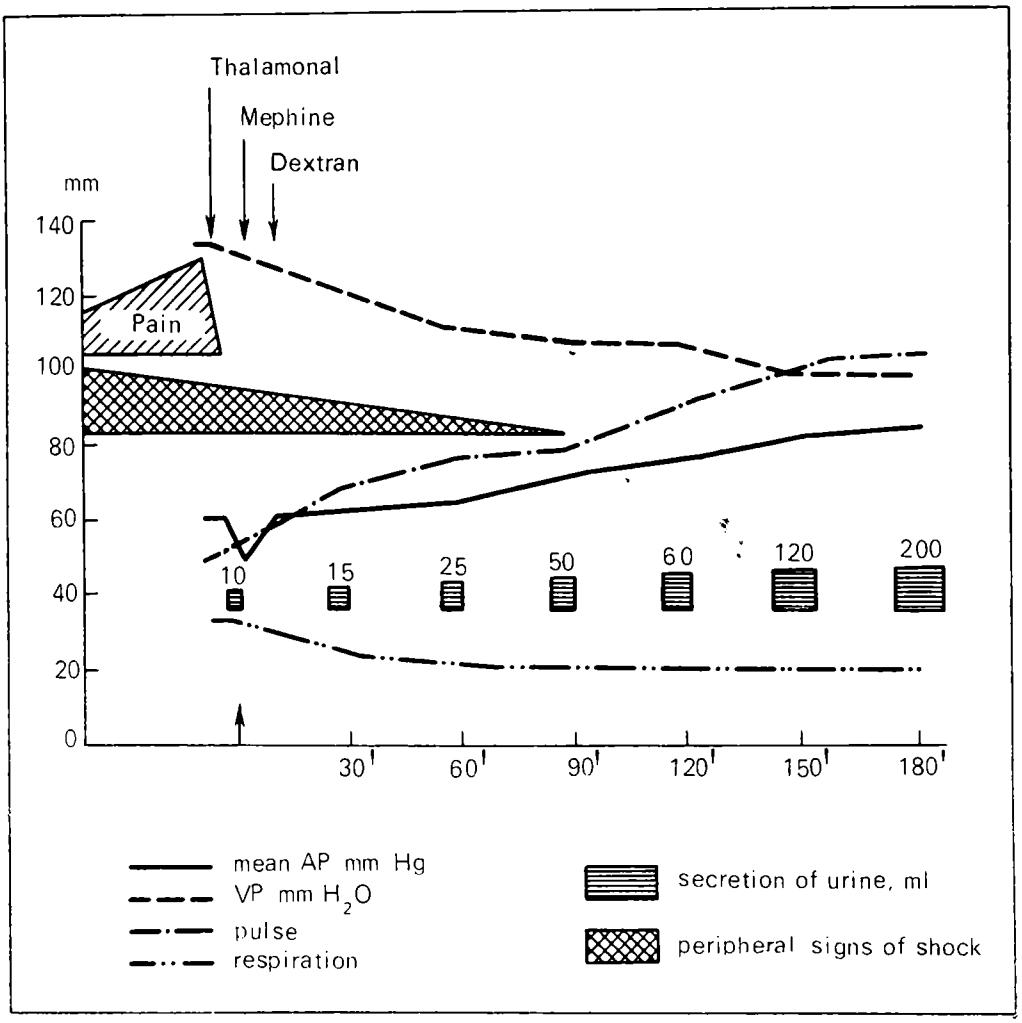

Fig. 80. Dynamics of some indices in a patient with myocardial infarction aggravated by cardiogenic shock on a background of treatment with thalamonal, mephin and low molecular dextran

itself. The system for counterpulsation consists of a cardiosynchronizer and a pump. At the Institute of Cardiology we studied jointly with Trubetskoi and Ruda the possibility of using the counterpulsation method in the treatment of collapse. We used the cardiosynchronizer developed by Kheifets, Gusarov and Konyaev, in accordance with the medicotechnical requirements of the Institute, and the pump designed by Margolin.

The cardiosynchronizer sends a working signal to the distributing device of the pneumatic pump whose chamber is a hermetically sealed reservoir with a movable membrane and one inlet (it also serves as an outlet). One of the main features of this system is strict synchronization of the work of the heart and the pump. From the arterial channel (through a catheter inserted in the femoral artery) the blood must be sucked into the chamber only during the systole and be ejected during the diastole. This leads not only to a decrease in systolic pressure which, as is known (Sarnoff *et al.*, 1958), decreases the work of the heart and the oxygen requirement of the myocardium, but also to an increase in coronary circulation due to the rise in diastolic pressure in the aorta.

Experimental studies have shown that upon counterpulsation on a background of lowered arterial pressure (after embolization of coronary arteries with mercury) the diastolic pressure in the aorta sharply increases (Ruda, 1967). In this case the coronary circulation also considerably increases (an average of 50 per cent). It is interesting that the function of the injured myocardium improved on a background of counterpulsation, namely the pressure in the left ventricle and the aorta increased, and the alternation of the force of cardiac contraction disappeared. The method of auxiliary circulation, which is just beginning to be used in the treatment of acute cardiovascular failure, is undoubtedly promising in the therapy of myocardial infarction.

Nevertheless, auxiliary circulation, apparently, will be unable completely to solve the problem of controlling cardiogenic shock. This is due to a number of technical difficulties (e.g. marked atherosclerotic affection of the peripheral arteries), and some fundamental problems. For example, in most cases of areactive shock the heart is so affected that it becomes incompatible with life. In such cases it is necessary to think of transplanting the heart or applying a prosthesis, while auxiliary circulation will be only an intermediate stage.

Of the other methods of treating collapse in myocardial infarction mention should be made (rather historical) of the attempts at intra-arterial pumping of blood. This therapy was based on the favourable effect it produced in traumatic shock. Surgery has accumulated sufficient experience of intra-arterial pumping in acute cardiovascular failure. But the mechanisms of such a failure differ from what is observed in cases of collapse during myocardial infarction. The main difference is that in collapse connected with myocardial infarction it is first of all the heart muscle that is considerably affected. In cases of traumatic shock, as was shown by the studies of Prof. Petrovsky's associates, pumping of arterial blood even into an isolated vessel causes a pressor reaction. On the other hand, pumping blood into an artery during myocardial infarction may not only improve the patient's condition, but also aggravate its severity in cases where the period of pumping coincides with the systole of the

heart because in these cases the load on the heart increases. Although some authors report the use of this method in the treatment of collapse during myocardial infarction, the findings in most cases pertain to very few observations and no convincing data in favour of using intra-arterial blood pumping are cited (Matusova and Morozova, 1958; Smetnev, 1966, and others).

The development of the most effective and rational methods of treating collapse largely depends on correct evaluation of the state of haemodynamics. For this reason we consider that the afore-discussed therapy must be administered under control of such methods which make it possible the most objectively to evaluate the state of haemodynamics and its changes under the action of various substances (studies of the blood-filling of various vascular regions by means of rheography, minute volume of the heart, arterial pressure, the mass of circulating blood, etc.).

Treatment of Arrhythmia

The appearance of arrhythmia in myocardial infarction considerably aggravates its course and is often the cause of death. There are cases of so-called arrhythmic collapses where it is possible to note, for example, a clear connection between the decrease in arterial pressure and the appearance of peripheral symptoms with auricular fibrillation, and other arrhythmias. The appearance of total block in myocardial infarction patients leads in half the number of cases to fatal results. As a rule, arrhythmias are also conducive to the development of cardiac failure. In connection with this, successful treatment, and especially prevention of various disturbances in rhythm, largely determine the prognosis in myocardial infarction. The possibilities of therapy in this field increase with each passing year. Fundamentally new methods of treatment, namely, electro-impulse therapy and electric stimulation, are effective methods of controlling such severe disturbances in rhythm as paroxysmal tachycardia and atrioventricular block. By acting on the disturbed electrolyte balance it is possible not only to put an end to some forms of disturbances in rhythm, but also to prevent their appearance.

Extrasystoles, paroxysmal tachycardias and cardiac fibrillation most commonly occur during the acute period of myocardial infarction. As Myasnikov pointed out, a certain role in the appearance of these forms of arrhythmias in myocardial infarction is played not only and not so much by the appearance of foci of necroses, as by the general disturbances in the metabolic and biochemical processes in the myocardium. This is confirmed by the higher incidence of rhythm disturbances during recurrent myocardial infarctions and during their appearance on a background of cardiosclerosis.

Our conceptions of the character and frequency of disturbances in rhythm have undergone a considerable evolution, especially of late, in connection with the introduction of the method of automatic

control of the electrocardiogram. Goldberg (1969) has shown that various forms of arrhythmia occur in 87.8 per cent of myocardial infarction cases. It is also important that among the patients who died these disturbances persisted until the very moment of death in 80 per cent of cases, whereas when the prognosis was favourable they ceased in 73.9 per cent of cases. The findings emphasize once again the significance of successful control of disturbances in rhythm for the prognosis in myocardial infarction. According to Lown *et al.* (1967) as a result of prophylactic administration of anti-arrhythmic substances, there was not a single case of cardiac fibrillation among these patients.

In evaluating the possibilities of preventing and treating arrhythmias in myocardial infarction from the pathogenic point of view it is necessary to distinguish two main trends in the elaboration of this therapy. The first one is associated with the use of substances which act directly on the disturbed electrolyte balance. By way of example we may cite the use of potassium salts, a 'polarizing' mixture. The second trend is characterized by a search for substances which suppress the increased excitability of the foci of ectopic automatism (e.g. novocainamide, gilurtymal).

In connection with the wider use of cardiac glycosides in the treatment of myocardial infarction some reports state that they are also effective in some rhythm disturbances. Myasnikov, Chernogorov, A. V. Vinogradov, Heinonen, Chazov, Szulc, and other authors observed a positive effect of strophanthin in some cases of paroxysmal tachycardia and cardiac arrhythmia. At first glance this is a paradoxical fact since it is known, for example, that various arrhythmias may appear on administration of large doses of strophanthin. Thus Parin and Fedorov (1966) report on the reproduction of paroxysm of ventricular tachysystole and cardiac fibrillation in dogs poisoned with strophanthin. However, the effect of strophanthin in some forms of arrhythmias may be explained with due regard for the modern views on the mechanism of its action.

It is known that cardiac glycosides in therapeutic doses inhibit the active return of potassium ions to the cell and the outgo of sodium from the cell into the extracellular fluid. The inhibition of active movement of the ions fosters liberation of the bound potassium from the membrane and sacroplasmic reticulum of the myocardial cell (Meerson *et al.*, 1968). All these electrolytic perturbations taking place in the myocardial cell on administration of strophanthin may favourably affect the biophysical processes which are conducive to the appearance of arrhythmias. Some role is also played by the activity of transport ATPase because the difference beween the therapeutic and toxic doses which causes disturbances in rhythm is manifested primarily by the extent of influence on this enzyme. Cardiac glycosides have an influence on cardiac excitability which is affected in myocardial infarction. Of some importance in the therapeutic action of cardiac glycosides is also their property to impede

atrioventricular conduction and prolong the refractory period. This is particularly important in the treatment of supraventricular arrhythmias (Doshchitsyn, 1968).

The changes in the myocardium under the influence of strophanthin or corglycon may lead to the restoration of the normal rhythm. This proposition is confirmed by experimental findings of Selavri (1958), and Aldinger (1967) who point out that administration of digoxin (12-hydroxydigitoxin; lanoxin) and other cardiac glycosides to animals prevents rhythm disturbances.

The effectiveness of strophanthin increases upon its slow drip administration. Particularly effective is administration of strophanthin or corglycon in a 5 per cent glucose solution with an addition of insulin and potassium. We usually administer 0.25 mg (0.5 ml of a 0.05 per cent solution) of strophanthin together with 200 ml of a 10 per cent glucose solution and 0.8-1 g of potassium chloride. Often the mixture of glucose, insulin and potassium, or the so-called polarizing mixture (Sodi-Pallares *et al.*, 1963), is administered without glycosides. We have already pointed out the role of altered electrolyte metabolism in the appearance of rhythm disturbances. It is well known, for example, that the process of myocardial excitation is based on an ionic mechanism. Successive increase in the concentration of potassium ions on the outer side of the cell membrane is accompanied with a decrease of both the electric potential and the excitation of the cell (Weidmann, 1956; Hoffman, 1959). There is a continuous exchange of potassium and sodium through the cell membrane between the intra- and extracellular fluid, 30 times as much potassium being contained in the cell as in extracellular fluid.

In studying the dynamic of potassium on administration of glucose and insulin some authors found that potassium moved from the extracellular fluid into the cell. According to the findings of Prinzmetal *et al.* (1961); Russel *et al.* (1961); Salmanovich (1961); Udelnov (1961) the appearance of a focus of necrosis is attended with a decrease in the content of intracellular potassium and an increase in the content of sodium in the cell. Such changes are conducive to the appearance of various disturbances in rhythm. In connection with this the attempts of a number of authors (Laborit *et al.*, 1954; Sodi-Pallares *et al.*, 1962; Brikker and Volpert, 1966; Mittra, 1966 and Yanushkevichus *et al.*, 1966) to influence the disturbed electrolyte metabolism in myocardial infarction for therapeutic purposes are justified. The experimental findings of Sodi-Pallares *et al.* (1962) showed that the mixture of insulin, glucose and potassium, by fostering the restoration of the potassium correlation between the cell and outside of it because more potassium enters the cell and is fixed in it, considerably improves the course of the disease and decreases, in particular, the frequency of rhythm disturbances. Subsequent clinical observations on administration of 1000 ml of a 5 per cent glucose solution with 40 mEq of potassium and 20 u of insulin confirmed the findings of the experiment.

According to Mittra (1966), the mortality among myocardial infarction patients given the 'polarizing' mixture was 50 per cent of that among the control patients. A mixture of glucose, insulin and potassium has of late been increasingly more widely used in the overall therapy of myocardial infarction in the USSR. Reference may be made to the reports of Yanushkevichus *et al.* (1966) who administered the 'polarizing' mixture of fibrinolysin, heparin and 20 ml of 25 per cent magnesium sulphate, and to Chernogorov and Kozhevnikov (1966) who, for the purpose of restoring the transmembrane gradient of potassium, administered, in addition to insulin and glucose, lydase (hyaluronidase) which increases the permeability of the cell membrane.

It should be pointed out that of late considerable importance in the appearance of arrhythmias has been attached not only to the changes in the potassium and sodium content, but also to other electrolyte disturbances. Thus Loeb *et al.* (1968) described two cases of ventricular fibrillation in connection with hypomagnesaemia. According to Reicherzt *et al.* (1967), administration of a complex of potassium and magnesium salts produces more encouraging results.

Today the 'polarizing' mixture is widely used by physicians of specialized first aid in the treatment of myocardial infarction patients for the purpose of terminating and preventing the disturbances in rhythm. Zilberman (1967) reports its successful use in conditions of first aid administered to 62 myocardial infarction patients.

It seems particularly important to us to use the 'polarizing' mixture for the purpose of preventing disturbances in rhythm. We associate the decrease in mortality noted by most authors who used the foregoing therapy precisely with the prevention of arrhythmias.

The analysis of our material (80 patients treated by the combination of glucose, insulin and potassium, and 80 patients treated without the 'polarizing' mixture) indicates that these groups differ in the frequency of rhythm disturbances. Particularly significant are the data obtained by continuous automatic control of the ECG. Both stable and transitory disturbances in rhythm, which usually escape the notice of the physician when other methods of observation are used, were more frequently recorded in the control patients. They often preceded more stable and severe disturbances in rhythm, including ventricular fibrillation. We did not observe any differences in the frequency and severity of cardiac failure, or the incidence of shock and thromboembolic complications between the control patients and those treated with the 'polarizing' mixture, but clearly noted the difference in mortality among the patients of these two groups. We therefore consider that the main action of the 'polarizing' mixtures is not so much in normalizing the rhythm, when it is disturbed, as in preventing arrhythmias.

Some authors are sceptical about the possibility of treatment with the 'polarizing' mixture. For example, Malach (1967) saw no

differences in the frequency of fatal results between the patients who received it and those who did not. Similar data are reported by Fletcher *et al.* (1968), Pentecost *et al.* (1968). Zhdanova *et al.* (1968) found no advantages in treatment with the 'polarizing' mixture over the other anti-arrhythmic agents.

Closely related to the treatment with 'polarizing' mixtures in the main mechanism of action is the method of treating and preventing arrhythmias with co-carboxylase. It is based on restoration of the metabolic processes operating in the heart muscle and disturbed in connection with myocardial infarction. Disturbance in carbohydrate metabolism, accumulation of lactic and pyruvic acids, in particular, are often observed in myocardial infarction. Bakumenko's studies (1966) have shown that accumulation of lactic and pyruvic acids and development of 'pyruvic' acidosis are conducive to the disturbances in rhythm. Co-carboxylase, as a co-enzyme, decarboxylates α-keto acids, pyruvic acid in particular, and thereby normalizes the carbohydrate metabolism and fosters a decrease in acidosis.

In a number of cases of myocardial infarction complicated by cardiac arrhythmia, and ventricular and atrial extrasystole, intravenous or intramuscular administration of 100-200 mg of co-carboxylase makes it possible to normalize the rhythm (Chazov *et al.*, 1964, and Bakumenko, 1966). Bakumenko notes that restoration of normal rhythm on administration of co-carboxylase is accompanied with a decrease in pyruvic acid in the blood.

Today we begin the treatment of practically all myocardial infarction patients with rhythm disturbances (atrial fibrillation and flutter, paroxysmal tachycardia and extrasystole) during the acute period with intravenous drip administration of a mixture consisting of 200 ml of a 5 per cent glucose solution, 100-150 mg of co-carboxylase, 10 u of insulin, 1 g of potassium chloride, 240 mg of vitamin B_1 and 150 mg of vitamin B_6. The administration of this complex is intended to normalize the bioelectric and biochemical processes disturbed in the affected myocardium and thereby to help in normalizing the rhythm.

In present-day practice of urgent and first aid novocainamide is the most widely used for the purpose of terminating the disturbances in rhythm. On appearance of rhythm disturbances during the acute period of myocardial infarction the substance is usually administered intravenously. Novocainamide (procainamine, pronestyl) is closely related to novocain and differs from it only by the presence of an amide group. Its anti-arrhythmic action is based on a considerable decrease in the excitability and conduction of the heart muscle. By depressing the automatism of both the ectopic centres and the sinus node, novocainamide affects the contractility of the myocardium much less than quinidine. On the appearance of various forms of tachycardiac arrhythmias in myocardial infarction 5 ml of a 10 per cent novocainamide solution (0.5 g) are administered intra-

venously. According to A. V. Vinogradov, who was the first in our country to use novocainamide in treating arrhythmias during myocardial infarction, the administration of this substance is sometimes accompanied with a decrease in arterial pressure. In view of this it is expedient to combine novocainamide with small doses of mesaton. If it proves ineffective, the substance is administered again in the same dose in 2 hours. The daily dose of novocainamide must not exceed 4 g. In milder cases novocainamide is given per os in a dose of 0.5 g 4 times a day. This method is less effective than intravenous administration of the substance, but is safer because it does not usually cause a decrease in the arterial pressure.

It is necessary to emphasize that in case of restoration of the rhythm novocainamide therapy should be continued in a maintenance dose of 0.5 g 3 times a day over a period of two to three weeks. However, the question of the duration of the treatment must be decided strictly individually, depending on the peculiarities of the pathological process. On the appearance of signs of intoxication—dyspeptic phenomena, headache, a sense of bitterness in the mouth—the treatment with novocainamide is discontinued. Contra-indications for the use of novocainamide are various disturbances in conduction because it inhibits conduction of impulses both in the atria and the ventricles. However, such changes arise only when large doses of the substance are given.

Numerous studies carried out in the last ten years both in our country and abroad have shown novocainamide to be quite effective in atrial fibrillation, paroxysmal ventricular tachycardia and extrasystole, which aggravate the course of myocardial infarction (Chernogorov, 1962; Shestakov, 1962; Chazov *et al.*, 1964; A. V. Vinogradov, 1965; Mikhnev *et al.*, 1966, and Lown *et al.*, 1967).

Literature contains reports on prophylactic use of quinidine and procainamide (novocainamide) during the acute period of myocardial infarction. While using these substances prophylactically Diordjevic and Bozinovic (1966) noted no decrease in the frequency of arrhythmias, but in patients given these substances the rhythm disturbances were less dangerous. According to Holmberg and Bergman (1967), quinidine decreases the frequency of arrhythmias when used prophylactically.

The question of the expedience of using these substances prophylactically in all myocardial infarction cases is debatable, especially considering that quinidine and novocainamide possess the property of decreasing the contractility of the myocardium. Our observations show that on the appearance of arrhythmia (paroxysmal cardiac fibrillation, group extrasystole) administration of novocainamide produces a positive effect not only by terminating the attacks of arrhythmia, but also by preventing their recurrence.

The method of electro-impulse therapy is being more widely introduced not only into the treatment of various rhythm disturbances in hospitals, but also into administration of first aid. The defibril-

lating effect of the pulse current in ventricular fibrillation was described as far back as the beginning of the 20th century. However, the extensive studies of this method, and especially its elaboration for employment in the clinic, were carried out by Gurvich (1957). It is precisely he who studied the optimally effective and safe parameters of the electric discharge. In the Soviet Union this method was for the first time used by Vishnevsky *et al.* (1959) during an operation on the heart aimed at terminating atrial fibrillations.

Despite the positive results produced by electro-impulse treatment of paroxysmal tachycardia and cardiac fibrillation connected with surgical intervention on the heart in cases of heart failure and cardiosclerosis (Effert and Grosse-Brockhoff, 1963; Oram *et al.*, 1963; Radushkevich *et al.*, 1964; Yanushkevichus and Shnipas, 1965; Lown *et al.*, 1967) it was very slowly introduced into the treatment of arrhythmias associated with myocardial infarction. There was an apprehension that the electric discharge might aggravate the main pathological process and impede the cicatrization of the myocardium. However, a series of experimental studies, and especially the development of apparatus for electro-impulse therapy with cardiosynchronization developed by Lown *et al.* (1967) made it possible to use this method in treating rhythm disturbances in myocardial infarction patients. The essence of the method is that an electric discharge of 4000-6000 V lasting up to 0.01 sec is passed through the thorax. The American authors considered it expedient to use discharges of lesser duration (0.001-0.005 sec), but higher voltage (8000-9000 V). Direct current is used because alternate current most commonly produces complications (considerable injuries to the myocardium and even ventricular fibrillation). However, single reports still appear (Bouvrain *et al.*, 1966) on the use of alternate current for electro-impulse therapy, which is considered to be more promising.

There are some differences on the question of using a cardiosynchronizer in electro-impulse therapy. It has been found that application of a discharge during a definite time of the cardiac cycle, precisely during the descending part of the *R* wave (Lown *et al.*, 1967), is the most effective and safe. Some Soviet authors (Zukerman, 1966; and others) consider the use of a cardiosynchronizer not necessary, noting that when they used the Gurvich apparatus in a large number of cases (Zukerman reports on 290 patients) they did not observe any severe complications such as ventricular fibrillations or focal changes in the myocardium. In our opinion, a cardiosynchronizer should be used in the treatment of arrhythmias in cases of myocardial infarction because some experimental studies mention the appearance of dystrophic and microfocal changes in the myocardium during unsynchronized electro-impulse therapy. Moreover, the probability of the development of ventricular fibrillation in myocardial infarction increases. Other authors (Syrkin and Maevskaya, Bogoslovsky, and others) arrived at the same conclusions.

Electro-impulse therapy is administered under anaesthesia. In

order to avoid possible complications the following, at first sight insignificant, but important conditions should be observed. For example, it is necessary to maintain a good contact of the surface of the electrode with the skin. For this purpose the surface of the skin must be thoroughly degreased, a pad of four or five layers of gauze moistened with hypertonic solution or a layer of electroconductive paste must be placed between the electrodes and the body, the electrodes must be well pressed to the body, etc.

If a complication, such as ventricular fibrillation, appears which occurs extremely seldom if all the rules are observed, it is necessary immediately to repeat discharge which usually restores the normal rhythm.

The speed with which the rhythm is restored and the slight probability of the development of complications make electro-impulse therapy one of the best modern methods of treating arrhythmias in myocardial infarction. The anti-arrhythmic action of the electric discharge is due to a simultaneous depolarization of the myocardium on a background of which the sinus node, the most powerful center of automatism, manifests its action.

The method of electro-impulse therapy is now beginning to be extensively introduced into practice. Its indications and contra-indications are being ascertained. Whereas in the first reports we stated, for example, that it was possible to make extensive use of this method in treating arrhythmias in myocardial infarction, today we have been convinced, on the basis of the studies carried out in our clinic (Bogoslovsky) that it is indicated, besides ventricular fibrillation, only in paroxysmal tachycardia and atrial flutter. In cases of cardiac fibrillation the effect is either absent or very unstable. Following electro-impulse therapy it is necessary to administer maintenance treatment with novocainamide in a dose 0.5 g 3 times a day.

The effectiveness of electro-impulse therapy in arrhythmias in the acute period of myocardial infarction is confirmed by the studies of Lukashevichute, Syrkin and Maevskaya, Bogoslovsky, Lown *et al.* and associates and other authors. Bogoslovsky discovered a considerable improvement of the haemodynamics in five myocardial infarction patients in whom the correct rhythm was restored by this method. In two patients, who were in a state of collapse after normalization of the rhythm, the arterial pressure increased. In 24 myocardial infarction cases where electro-impulse therapy was used Schroeder *et al.* (1967) found the method to be safe when a cardiosynchronizer was used and highly effective, especially in paroxysmal tachycardia.

Yanushkevichus and Schnipas (1967) suggest using electro-impulse therapy in the later period of myocardial infarction, i.e. four or six weeks after the onset of the disease. At the same time a positive haemodynamic effect of electro-impulse therapy was observed in restoration of the rhythm, namely, a considerable increase in the

minute volume of the heart and the rate of blood flow. We therefore think that earlier utilization of electro-impulse therapy may prevent circulatory failure.

Zilberman (1967) reports the use of electro-impulse therapy in conditions of the first aid. He obtained very encouraging results, namely, a positive effect in 88 per cent of cases of various arrhythmias appearing in the acute period of myocardial infarction. The author does not mention the duration of the effect, but his findings make it possible to recommend extensive use of electro-impulse therapy in conditions of the first aid. This is the more important since the rhythm disturbances appearing during the acute period of myo-

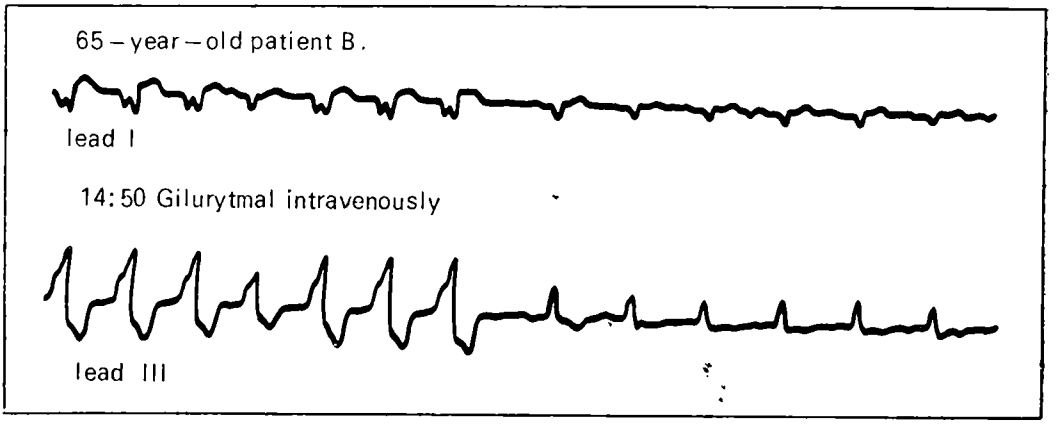

Fig. 81. Normalization of the cardiac rhythm under the influence of gilurytmal

cardial infarction considerably aggravate the course of the disease and may be conducive to the development of collapse and ventricular fibrillation.

Of the other methods of treating arrhythmias in myocardial infarction being elaborated today mention should be made of using blocking agents of β-adrenergic receptors, e.g. inderal (propranolol).

The mechanism of action of the blocking agents of β-adrenergic receptors has not as yet been completely elucidated. Most authors emphasize the many-sided character of their action and the impossibility of reducing the effect exclusively to the sphere of blocking the adrenergic reactions (Braunwald, 1966; Wolfson *et al.*, 1966; and Trubetskoi, 1967).

The anti-arrhythmic action may be connected not only with blocking the adrenoreactive structures. It is due probably to a greater extent to the delay of the phase of rapid depolarization of the action current of myocardial fibres, intensification of the vagal reactions of the heart (Trubetskoi), direct depressing action of the substance of the heart. Shkhvatsabaya *et al.* (1967) hold that inderal acts like quinidine. Literature contains many reports on the use of inderal in the treatment of coronary failure and hypertension, and in controlling the rhythm disturbances (Katz, 1965; Fröhlich *et al.*,

1966; Schroeder *et al.*, 1966; Moiseev and Ustinova, 1967; Shkhvatsabaya *et al.*, 1967; Doshchitsyn, 1968).

However, despite the large number of reports, there are as yet no sufficiently clear ideas of the effectiveness of inderal in any particular rhythm disturbances. Nor is there a single opinion on the optimum doses. For example, Lukomsky *et al.* (1967) note a positive effect in cardiac fibrillation with ventricular tachysystole in myocardial infarction patients on intravenous administration of 5-10 mg of inderal. The same doses were used by Shkhvatsabaya *et al.* (1967) and Schamroth (1966) who observed a positive effect of the preparation in paroxysms of cardiac fibrillation, sinus and ventricular tachycardia. Some authors consider inderal to be the most effective in paroxysmal and sinus tachycardia, recommending caution in its intravenous administration. The treatment should be begun with a dose of not more than 1 mg. In the absence of effect the administration may be repeated in 5 min. The substance may also be administered per os in a daily dose of 60-200 mg. Nielsen and Jörgensen (1966) note that inderal is ineffective in cases of cardiac fibrillation.

We administered inderal intravenously in a dose of 5 mg for the purpose of terminating various rhythm disturbances in 16 patients and could not find a reason to prefer this method to the existing ones (strophanthin, novocainamide, electro-impulse therapy). On the other hand, inderal produces a number of side effects which limit its administration in myocardial infarction. This is first of all a decrease in myocardial contractility and in arterial pressure (Luria *et al.*, 1966, and Wennevold and Sandoe, 1966) which exclude the use of inderal in cases of collapse and in the presence of signs of congestive cardiac failure. However, we must agree with Lukomsky who favours the use of inderal in myocardial infarction as an agent that prevents severe rhythm disturbances and cardiac fibrillation.

Isoptin (verapamil), the use of which was reported in the Soviet press (Doshchitsyn *et al.*, 1967) belongs to the group of blocking agents of β-adrenergic receptors. Possessing less marked β-blocking action than inderal it is effective in cases of paroxysmal tachycardia and cardiac fibrillation. Isoptin is administered both intravenously (5 mg) and per os in a dose of 120-200 mg a day. Some of our findings warrant an assertion against its use in the acute period of myocardial infarction. As a matter of fact, in addition to its anti-arrhythmic action, it may cause a certain decrease in myocardial contractility and arterial pressure.

Of the other substances the use of which in the treatment of arrhythmias connected with myocardial infarction is now being discussed mention should be made of ajmalin (gilurytmal). It is one of the alkaloids of Rauwolfia, is closely related to quinidine in the mechanism of its anti-arrhythmic action, but is much less toxic. It decreases the permeability of the cell membranes, prolongs the refractive phase of the heart and reduces the excitability of the myo-

cardium. In questions of the effectiveness of this substance in myocardial infarction there is still much that is unclear and debatable. For example, Schroeder *et al.* (1967) administered it to 31 patients with various rhythm disturbances which aggravated the course

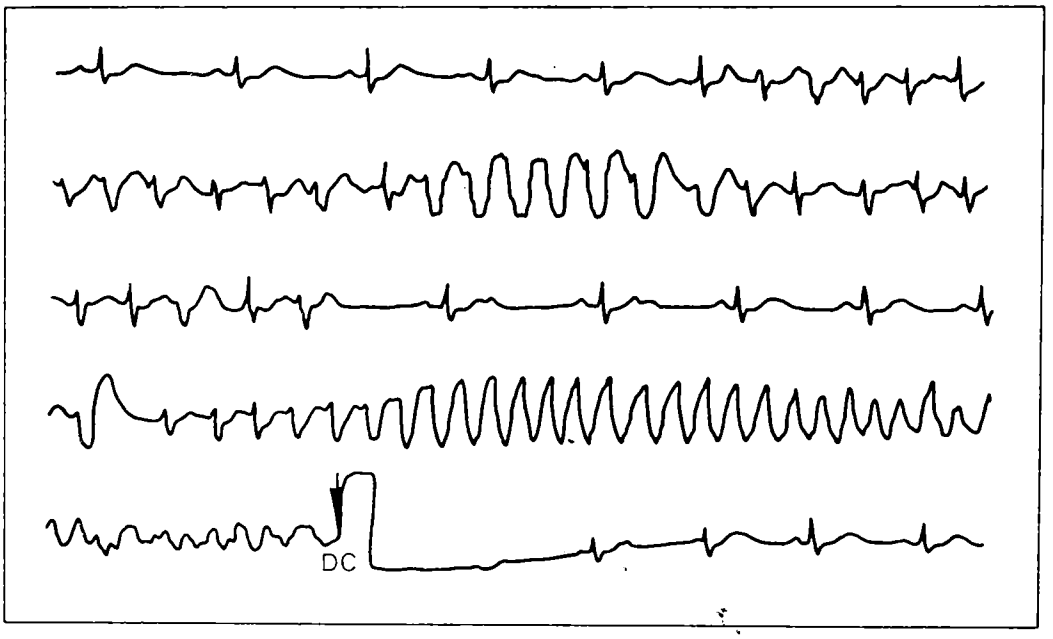

Fig. 82. Severe rhythm disturbances developing into ventricular fibrillation in a patient with an acute myocardial infarction. Restoration of the sinus rhythm after electric defibrillation (indicated by an arrow)

of myocardial infarction. By administering gilurtymal either by prolonged infusion in a dose of 600 mg a day or of 100 mg every 4 hours perorally they observed a positive effect in most cases, especially in ventricular extrasystole. Doshchitsyn reports administration of the preparation in a single dose of 50 mg (150-300 mg a day). Gilurtymal is considered the best maintenance agent after electroimpulse therapy. Its effectiveness is confirmed by the findings of a number of authors (Benda *et al.*, 1966, and Lampugnani, 1967) (Fig. 81).

Fairly good results are obtained only on intravenous administration of the substance. In a number of cases even a small dose (50-60 mg) restored the correct rhythm (Forster and Holzmann, 1967). Ajmalin, as we have already pointed out, is the most effective in paroxysmal tachycardia and ventricular extrasystole, less effective in cardiac fibrillation and atrial flutter, and useless in cases of prolonged disturbances in rhythm. However, the available experience of using ajmalin in the treatment of rhythm disturbances in myocardial infarction is as yet inadequate to draw any conclusions on its effectiveness. The results of the observations conducted in the Soviet Union mainly coincide with the findings of foreign authors concerning the use of gilurtymal.

Treatment of Disturbances in Cardiac Conduction

The development of myocardial infarction may be accompanied with the disturbances in cardiac conduction. From the standpoint of effectiveness of the treatment and prognosis it is important to emphasize the different causes which may account for the disturbance in conduction. It may be due to direct affection of the conduction paths as a result of their necrosis, the metabolic and biochemical changes in the paranecrotic zone, if the conduction paths are in this zone (Udelnov's phenomenon) and neurogenic influences. Whereas the chances of restoring the normal rhythm by usual medicinal substances are insignificant in the first case, this possibility is retained in other cases.

Atropine is the oldest agent which is used primarily when conduction disturbances are found. Its action is aimed at reducing the tone of the vagus nerve, which results in acceleration of the wave of excitation passing along the conduction system, especially along the atrioventricular part (Chernogorov, 1962). We usually administer atropine subcutaneously or intravenously in doses of 0.5-1.0 ml of a 0.1 per cent solution one or two times a day.

Of the other relatively old and therefore more widespread methods of therapy mention should be made of the use of adrenalin and related substances (ephedrine, isadrin). They are used in various degree of atrioventricular block, including total block. The mechanism of their action comes down to their influence on the metabolic processes operating in the conduction paths and the zone surrounding them. It should be mentioned that the regulatory influence of the sympathetic nervous system on the heart fully manifests itself in cases of sufficient catecholamine content in the myocardium. The development of myocardial infarction is accompanied with a decrease in catecholamines in the heart muscle. It is possible that the administration of adrenalin and other substances, by compensating for this insufficiency, normalizes the function of the conduction system of the heart. As concerns the dose of adrenalin for treating the disturbances in atrioventricular conduction, the opinions differ. Chernogorov recommends in these cases the use of small doses of adrenalin (e.g. 50 ml of adrenalin solution in 1 : 200 000 dilution, in enema). In total block with frequent Morgagni-Adams-Stokes attacks he suggests subcutaneous or intravenous administration of adrenalin in a 1 : 1000 dilution in a dose of 0.2 ml every 3-4 hours 3 times a day. Other authors recommend these doses for all cases of conduction disturbance. Dolgoplosk and Shadur (1955); Plots (1961); Chernogorov (1962), and Votchal (1963, 1965) used ephedrine in the treatment of conduction disturbances. They recommend administration of ephedrine in a dose of 0.025 g per os 3-4 times. Plots administered such doses every four hours. It is necessary to control the ECG and arterial pressure. Moreover, it is expedient to combine these substances with atrophine.

Isadrin (isoprenaline), which is a noradrenalin derivative, is being used of late to treat rhythm disturbances. Isadrin and the related drug isuprel increase the excitability of the myocardium more than does adrenalin. There is less chance that ventricular fibrillation may appear when these substances are used than upon administration of adrenalin. Isuprel is administered sublingually in a dose of 10-30 mg and subcutaneously in a dose of 0.2 mg. It may also be given intravenously (by the drip method). Isadrin is administered sublingually in a dose of 5-10 mg.

A number of studies conducted by Soviet (Chernogorov, 1962; Mikhnev *et al.*, 1966, and others) and foreign (Natanson, Miller) authors report an acceleration of rhythm under the influence of these substances even in total atrioventricular block. Votchal and Grigorov (1968) used euspiran, a substance closely related to isuprel, to treat 48 patients with disturbed atrioventricular conduction. In administering it sublingually in a dose of 10-20 mg they noted restoration or improvement of atrioventricular conduction in eight patients. Moreover, the Morgagni-Adams-Stokes attacks either disappeared or became much less frequent in 21 patients.

Steroid hormones have of late been more widely used in treating the disturbances in conduction. Their use is based on the possibility of reducing the inflammatory phenomena which may involve into the process the conduction paths in the paranecrotic zone.

As far back as 1955 Lown *et al.* showed that administration of cortisone to patients affected with Addison's disease resulted in the disappearance of the conduction disturbances characteristic of this disease. We are inclined to associate the effect of steroid hormones in myocardial infarction to a greater extent with their anti-inflammatory action, although in this affection we cannot exclude hormonal insufficiency as a factor contributing to the development of conduction disturbances.

A large number of reports on this method of treating conduction disturbances has appeared in Soviet literature (Chernogorov, 1962; Votchal, 1963; Mikhnev *et al.*, 1966, and Uzbekova, 1967). It is considered more expedient to begin the treatment with large doses of hormones. Prednisolone is administered in a dose of 50-80 mg which is subsequently gradually decreased. Hormones are also used in conditions of first aid for treating conduction disturbances. For example, Mikheev *et al.* (1966) report the use of prednisolone by physicians of anti-infarction teams, who begin the treatment with intravenous administration of 30 mg of prednisolone and then injected intramuscularly 50-75 mg of hydrocortisone. Zilberman (1967) reports a positive effect of this therapy in 22 of 49 patients. We most commonly employ combined treatment aimed at various mechanisms of conduction disturbances (both neurogenic factors and the inflammatory process), and also atropinization and hormones (Fig. 83).

The elaboration and introduction into clinical practice of electric

stimulation of the heart should be considered a great achievement of modern cardiology. This method is particularly important in complete transverse block in which it is often the only way to save the patient's life. A necessity of urgent electrostimulation of the heart may arise in myocardial infarction, especially in the acute period. Two methods may be used in these cases.

The first method is transvenous intracardial electrostimulation of the heart; being atraumatic it is most promising. It is now widely used and continuously improved. It consists in introduction of an active electrode into the cavity of the right ventricle and an indifferent electrode under the skin of the neck. Electrostimulation is conducted from a generator located outside the body. Some authors use a biopolar catheter—electrode, in which case it is not

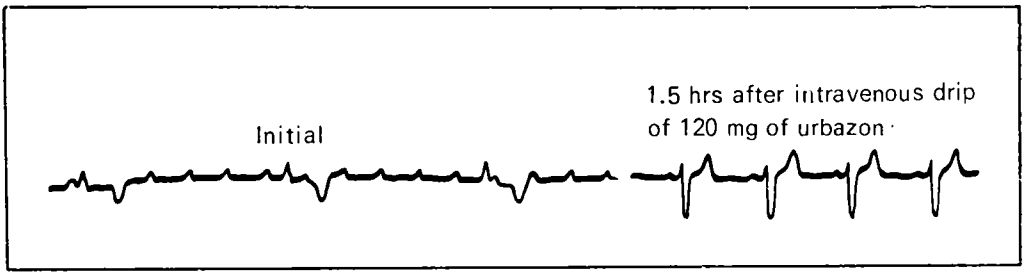

Fig. 83. Influence of steroid hormones on the disturbance in atrioventricular conduction in a patient with acute myocardial infarction

necessary to introduce the indifferent electrode under the skin. Bjorck *et al.* (1967) used this method in 18 myocardial infarction patients and noted good results.

The second method consists in introduction of a wire electrode through a puncture in the left ventricle and subsequent removal of the needle after introduction of the electrode (Bakulev *et al.*, 1966). The appearance of frequent Morgagni-Adams-Stokes attacks serves as an indication for such urgent electrostimulation of the heart. Subsequently, according to indications, electrodes are implanted in the myocardium for continuous stimulation of the heart or the latter is carried out by means of the same transvenous electrode which is connected to a portable generator implanted under the skin. A platinum electrode inserted by means of a mediastinoscope may also be used. However, this operation is quite traumatic and must be used after myocardial infarction with caution.

Considerable experimental and clinical material confirming the effectiveness of using electrostimulators and the good prospects of this method has now been accumulated (Saveliev *et al.*, 1967) (Fig. 84).

Treatment of arrhythmias in myocardial infarction is fairly complicated. The introduction of new methods of therapy has consider-

ably extended the physician's possibilities and improved the prognosis of myocardial infarction. In should be emphasized that control of arrhythmias is at the same time an important factor in preventing ventricular fibrillation and circulatory failure.

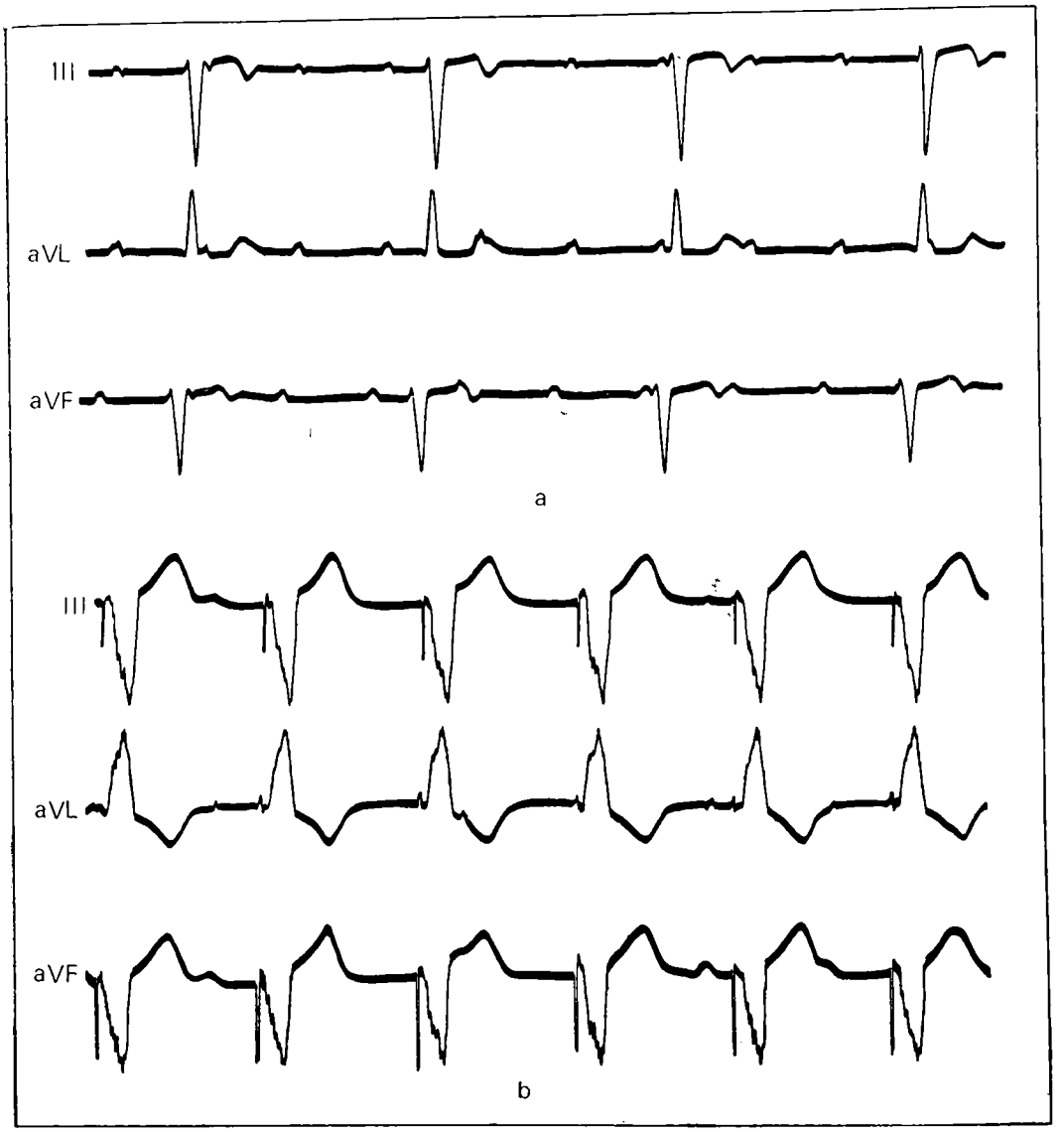

Fig. 84. Electrostimulation of the heart by means of a bipolar electrode in a patient with myocardial infarction and total transverse block
a—before electrostimulation;
b—on a background of electrostimulation (frequency 80 per min)

Treatment of Heart Failure

Effective and rational therapy of heart failure in myocardial infarction is possible only when the mechanisms of this complication of infarction are sufficiently deeply understood. Every case of myocardial infarction may be accompanied with heart failure. Whether

this will take place or not largely depends on the organism's compensatory potentialities, the cardiovascular system in particular. However, compensation is effected not only by the haemodynamic changes but also by the appropriate reactions of hormonal, enzymatic, electrolytic and other factors. The studies carried out by our co-workers point out changes in catecholamines, renin, and aldosterone in myocardial infarction which not only regulate the vascular tone, but also affect the organism's sodium and water metabolism. All this must be taken into consideration in the treatment of heart failure in myocardial infarction patients.

From the standpoint of the therapy of heart failure in myocardial infarction we distinguish two of its forms or syndromes. The syndrome of acute heart failure developing during the first hours and days of myocardial infarction and most commonly manifested in pulmonary oedema is characterized primarily by a rapid and considerable decrease in myocardial contractility. A certain role is also played by a decrease in the organism's compensatory potentialities manifested, in particular, by an increased tone of the peripheral vessels which is not sufficient for maintaining arterial pressure on an adequate level. In a large number of cases these changes develop on a background of normal energy potentialities of the unaffected myocardium.

The second form, or syndrome, of chronic heart failure is characterized by marked metabolic disturbances in the myocardium and changes in the water and salt metabolism. In connection with the exhaustion of the compensation functions of hypertrophied intact parts of the myocardium an outflow of potassium from its cells, a decrease in the content of vitamins B_1 and B_6 in the heart muscle and a decrease in the ATP content are observed (Meerson, 1960). All these changes considerably reduce the energy potentialities of the myocardium. The syndrome of chronic heart failure may also develop from the acute form and it is very difficult to differentiate this transition. The appearance and transition of one form to another greatly differ in time and are strictly individual. In some cases, especially during onset of myocardial infarction on a background of the already altered heart muscle, the signs characteristic of the syndrome of chronic heart failure may appear already in the first days of the disease.

Studies of the pathogenic features of heart failure in myocardial infarction enable us to state the fundamental propositions concerning the most effective schemes of treatment. The most characteristic feature of the syndrome is a sudden and marked decrease in the contractility of the myocardium. In these cases the therapy must therefore be aimed primarily at increasing the propulsive capacity of the heart and the contractile potentialities of the intact parts of the myocardium. On the basis of this cardiac glycosides, i.e. strophanthin, corglycon, etc., should be the main therapeutic agents.

Despite the fact that digitalis has been used in the treatment of circulatory failure for about 200 years and strophanthin (in our

country) for more than 60 years (Strazhesko, 1910) the questions of treating with them the heart failure connected with myocardial infarction are being continuously debated. We still remember the caution bordering on fear with which physicians regarded administration of strophanthin during the acute period of myocardial infarction and the statements pertaining to deterioration of the coronary circulation and increase in the incidence of myocardial ruptures on using cardiac glycosides.

The introduction of the method of early hospitalization and employment of specialized first-aid teams in the treatment of myocardial infarction patients contributed to more extensive use of strophanthin and other substances of this group in myocardial infarction complicated by heart failure or shock. Numerous observations have revealed the groundlessness of limiting the use of strophanthin and corglycon in myocardial infarction. These findings warrant once more the assertion of the necessity of carefully applying to the treatment of human patients the data obtained, as a rule, in experiment on healthy animals. The experimental conclusions must be verified by extensive clinical experience.

The experiments (Veselova, Wegria, and others) and clinical findings (Slutsky *et al.*, Plots, Malmcrona *et al.*) not only indicate the absence of the unfavourable effect of strophanthin and corglycon on the coronary circulation, but also do not exclude the possibility of their coronary dilatative action. In none of the 150 myocardial infarction patients to whom we administered strophanthin and whom we specially watched to see the effect produced by cardiac glycosides on coronary failure did we note the appearance or aggravation of its signs. Votchal and Slutsky (1967) using objective criteria of evaluating the coronary blood flow did not find any deterioration in the coronary circulation on administration of strophanthin. The mechanism of action of cardiac glycosides is debatable in many respects. The only fact that does not rise to any doubts is that for the action of strophanthin or corglycon to be manifested the heart muscle must contain sufficient amount of the so-called energy substances. The energy potential of the intact myocardium is most commonly sufficient in the acute heart failure syndrome. Only in recurrent myocardial infarctions or on the appearance of necrotic changes on a background of marked cicatricial and cardiosclerotic processes the glycosides are less effective.

The criteria of the effectiveness of cardiac glycosides are very important. In marked cases they are not difficult to determine. For example, the disappearance of the symptoms of pulmonary oedema or congestive phenomena in the lungs serves as the best index of the therapeutic effectiveness of cardiac glycosides. In cases of mild heart failure there are as yet no sufficiently clear objective criteria for evaluating their action. To establish such criteria we (Pushkar *et al.*, 1964) studied the phases of the cardiac cycle in using glycosides and in a number of cases were able to differentiate the

forms of heart failure quite readily amenable to treatment with strophanthin or corglycon and those where the treatment with only these substances could not be effective.

As we have already pointed out, the action of cardiac glycosides on myocardial structures and the heart's conduction system is very individual and the difference between therapeutic and toxic doses is often negligible. At the same time the influence of these preparations on the ion metabolism in the heart muscle and on the function of some enzymes is fraught with a danger of disturbing the rhythm and conduction. These findings are especially demonstrative and were obtained on using a monitor system with continuous automatic control of the ECG. On administration of cardiac glycosides we observed various transient rhythm disturbances to the point of ventricular fibrillation. In myocardial infarction glycosides must therefore be administered with caution. Their introduction into the treatment of these patients was undoubtedly a turning point in the fate of those whose condition was aggravated by heart failure. The necessity of individualizing the doses of glycosides must be emphasized once more. Of late, in rendering first aid, we encounter cases where, in order to produce an effect at the different stages of the treatment, we administered divided doses amounting to 2-2.5 ml of a 0.05 per cent strophanthin solution (1-1.25 mg) a day and did not observe any side effects. At the same time there were cases of glycoside intoxication on administering much smaller doses, i.e. 0.5-0.75 ml of a 0.05 per cent solution (0.25-0.4 mg) (see Fig. 79).

Concerning the use of glycosides in the acute period of myocardial infarction we must dwell on the methods of administering these substances. It is well known (Mashkovsky, 1967), that strophanthin and corglycon are fairly quickly eliminated from the organism and the maximum of their action occurs between the first and second hour. Their stream administration, therefore, produces quite rapid, but, at the same time, transient effect. Usually we administer a slow intravenous drip infusion of these substances. The observations carried out by our co-workers under control of a number of haemodynamic indices indicate that with this method of administering cardiac glycosides the increase in the minute volume is somewhat slower (over 20-30 min), but more strongly pronounced and, what is the most important, stable. By prolonging the administration of strophanthin or corglycon to 2-2.5 hours it is possible to make the effect of the substance longer.

As we have already pointed out, the action of cardiac glycosides is attended with changes in the electrolyte metabolism in the myocardium and the functions of certain enzymes which are sometimes conducive to rhythm and conduction disturbances. Prevention of the toxic action of glycosides, therefore, undoubtedly extends the possibilities of using them. In the chapter on the treatment of arrhythmias we cited data on combined use of strophanthin or corglycon with a polarizing mixture and a number of other substances

which affect the electrolyte balance and the metabolism in the myocardium (co-carboxylase, vitamin B_1 and B_6). Their use decreases the frequency of rhythm and conduction disturbances, developing in connection with administration of glycosides, nearly 50 per cent.

One of the causes of the toxic action of cardiac glycosides is blocking the sulph-hydryl groups of adenosine triphosphatase. Restoration of the activity of this enzyme owing to the increase in the content of sulph-hydryl groups in the myocardium leads to disappearance of the signs of intoxication (Meerson *et al.*, 1968). This proposition was confirmed by an experiment of using unithiol (dimercaptopropane sulphonate), one of the donators of sulph-hydryl groups in glycoside intoxication. Unithiol, an antidote, used in poisonings with heavy metals, contains two sulph-hydryl groups and is a potent donator of these groups. Its use in the clinic (Klykov, 1969; Chazov, 1970) demonstrated the effectiveness of the substance in rhythm and conduction disturbances connected with intoxication with cardiac glycosides. We usually administer 5 ml of a 5 per cent unithiol solution twice a day during the first two days, and subsequently once a day. Meerson *et al.* (1968) observed the disappearance of ventricular extrasystole in 17 of 20 patients and bigeminy in 10 of 12 patients on a background of this therapy. Our findings also confirmed the effectiveness of unithiol treatment.

The syndrome of acute heart failure often resembles pulmonary oedema which is a peculiar concentration of changes that occur in heart failure connected with myocardial infarction both in the heart itself and in a number of other organs and systems. This pertains to water metabolism, changes in the tone of the pulmonary vessels, oxygenation of tissues, etc. For this reason therapeutic measures are necessary aimed not only at increasing the contractility of myocardium (administration of cardiac glycosides), but also at decreasing the mass of circulating blood, enhancing oxygenation, and normalizing water metabolism. All this accounts for the difficulties which physicians encounter in treating patients with pulmonary oedema that considerably aggravates the course of infarction. Until recently mortality in cases of this complication amounted to 50 per cent (Plotz, 1961).

The administration of cardiac glycosides, i.e. strophanthin, corglycon, etc., have always been an important therapeutic measure in pulmonary oedema. Considerable importance is being attached of late to a decrease in the mass of the circulating blood. The old method of blood-letting is an example of such an influence. Despite the fact that some authors (Shestakov, 1957; Plotz, 1961; and Luisada, 1964) consider it expedient to bleed patients during pulmonary oedema connected with myocardial infarction, we regard this suggestion with great caution. The removal of 100-150 ml of blood does not substantially affect the mass of circulating blood, but may cause, although infrequently, marked vascular disturbances of a reflex nature with a subsequent decrease in arterial pressure.

This is the more important to take into account since in each case of myocardial infarction there is a potential danger of the developing collapse. We usually resort to blood-letting only in cases of fairly high arterial pressure (not lower than it was before the disease).

In order to affect the mass of circulating blood during pulmonary oedema diuretics are used. Novurit (mercurophylline) administered intravenously in a dose of 0.5-1.0 ml is rather effective. However, this method has not become widespread because of the apprehensions that administration of mercurial diuretics will aggravate the renal disturbances often developing during myocardial infarction. Lasix (furosemide) is more extensively used today. Possessing marked diuretic action lasix, according to a number of authors (Stokes, 1964; Kiessling, 1965, and Sidorenko, 1966), exerts a positive influence in pulmonary oedema. Unlike hypothiazide, for example, the important property of lasix is that it does not appreciably alter the excertion of potassium. Of the 25 myocardial infarction cases in which we used lasix and examined the content of potassium in the blood plasma we observed its decrease only in one case.

As the observations of our coworkers (Zysko *et al.*, 1966) show, lasix is effective only in cases of pulmonary oedema during myocardial infarction in which the arterial pressure is not sharply reduced. We explain this fact by a decrease in glomerular filtration during shock, which prevents the manifestation of the diuretic action of lasix. We usually administer 40-120 mg of lasix intravenously.

Of the other diuretics mention may be made of hypothiazide (hydrochlorothiazide). But its relatively slow diuretic effect does not warrant its recommendation as a first-aid agent in pulmonary oedema.

Reports on using urea in treating pulmonary oedema have been appearing of late. Its use is based on the marked dehydrating action which is successfully used in controlling cerebral oedema, in terminating acute attacks of glaucoma, etc. In 25 cases of myocardial infarction complicated by severe pulmonary oedema, where preliminary treatment with strophanthin, morphine and diuretics proved ineffective, our co-workers (Zysko and Ruda) used urea. In 11 patients pulmonary oedema occurred on a background of a severe cardiogenic shock. A specially purified urea preparation was used from which a 30 per cent solution had been made ex tempore. Urea was administered in a 5 per cent glucose solution on the basis of 1 g per 1 kg of the patient's weight over a period of 1-1.5 hours. After urea, in order to correct the acid-base balance, sodium bicarbonate was administered by the intravenous drip method. An immediate positive effect was noted in 14 patients which was manifested by a decrease in dyspnoea, the disappearance of gurling respiration and by the considerably decreased rales in the lungs. The introduction of this method will undoubtedly improve the pro-

gnosis in pulmonary oedema, which is confirmed by the findings of other authors. We observed a certain increase in residual nitrogen in the blood in all cases of urea administration, which persisted for 24 hours in two-thirds of the cases. We therefore consider that urea is contra-indicated for patients with kidney affection. It is as yet difficult to speak of the mechanisms of action of urea in pulmonary oedema. It is only evident that the effect is connected not only with diuretic action which is negligible (not more than 300-400 ml during the immediately following two hours). The inotropic influence of urea on the myocardium and the dehydrating action on pulmonary tissue are more probable. However, these propositions require further investigation, experimental study in particular.

The method aimed at improving pulmonary oxygenation have of late been more widely employed in the therapy of pulmonary oedema. Whereas oxygen therapy by means of anaesthetic and respiratory apparatus and specially centralized systems in hospitals are successfully used in the treatment of pulmonary oedema, the methods aimed at improving the patency of the respiratory tract in this condition are known much less.

An important role in the mechanism of the development of pulmonary oedema is played by a passage of a protein-rich fluid into the lumina of the alveoli. In passing through it the air forms a large amount of foam which disturbs the movement of air in the respiratory tract and thereby aggravates the state of hypoxia. Rapid destruction of the foam in pulmonary oedema not only improves oxygenation, but also often prevents death from asphyxia. To destroy the foam, antifoaming agents are used, i.e. substances which owing to their physicochemical properties foster the destruction of foam. The best known antifoaming agent is ethyl alcohol. Shestakov (1962), Luisada and Rosha (1964), and other authors report good results obtained by inhalation of alcoholic vapours produced either by the mask method or through a nasal catheter. A 70-96° alcoholic solution is usually used with either oxygen or air passed through it.

In our clinic Zysko, Ruda and Trubetskoi were the first to employ antifoamsilain, as an active antifoaming agent commonly used for destroying the foam in apparatus of artificial circulation. The observations carried out in a number of first-aid cases (Rudneva, 1965) showed that on inhalation of vapours of antifoamsilain, which was poured into the humidifier of the respiratory apparatus as a 10 per cent alcoholic solution, the foam disappeared from the respiratory tract in a few minutes. The oxygen or oxygen-air mixture, which was given to the patient through the mask, carried the vapours to the patient's respiratory tract in passing through the antifoaming agent's solution. The inhalation was begun after the foam from the oral and nasal cavities was previously removed. Foam elimination is a symptomatic method of treating pulmonary oedema and must play an important role in the complex of therapeutic measures.

The introduction in our clinic of new methods of treating pul-

monary oedema (antifoamsilain, lasix, urea, etc.) enabled us to reduce the number of fatal results from this severe complication of myocardial infarction nearly 30 per cent.

In the chronic heart failure syndrome, which may develop during the very first days of myocardial infarction, a considerable decrease in the energy potential of the myocardium comes to the fore and leads to a decrease in myocardial contractility. In view of this the therapy must envisage administration not only of substances, which enhance the contractile properties of the myocardium (strophanthin, corglycon), but also substances capable of increasing the energy potential of its cells. The simplest method is administration of insulin with glucose, which, as we have already pointed out, influence the state of the cell membranes and improve the carbohydrate metabolism in the myocardium. The same thing may be said about B vitamins group (B_1 and B_6) whose deficit in the myocardium is observed in the chronic heart failure syndrome.

It is also necessary to dwell on the possibility of using ATP in such cases. These is an opinion that in myocardial infarction administration of ATP is contra-indicated. However, it is based largely on assumptions and not on concrete clinical findings. We consider it expedient to administer it in cases of chronic heart failure arising in connection with myocardial infarction in a dose of 1 ml of a 1 per cent ATP solution twice a day intramuscularly or Hungarian corhormone, which is an extract from the heart and embryos, in a dose of 2 ml once a day intramuscularly. Observations on more than 50 patients have shown that this preparations considerably improved the course of myocardial infarction and reduced the manifestations of heart failure. We did not observe any side effects of ATP.

In discussing the treatment of the chronic heart failure syndrome aimed at normalizing the disturbed metabolic processes in the myocardium and at restoring myocardial contractility it is necessary to point out the new trend in this field connected with the use of co-factors of the synthesis and precursors of nucleic acids (Lukomsky, Meerson *et al.*). Daily administration of 1.5 g of orotic acid, 60 mg of folic acid and 100 mkg of vitamin B_{12} to myocardial infarction patients considerably decreased the incidence of heart failure compared with the control patients. Whereas not a single treated patient died of heart failure, in the control group there were seven cases of death from progressive heart failure. The administration of co-factors of synthesis and percursors of nucleic acids, which, in addition to the foregoing, also include methyl-uracil, is supposed to activate the synthesis of nucleic acids and proteins. Hyperfunction of the heart appearing in connection with the affection of the myocardium is usually accompanied with an activation of the synthesis of nucleic acids and proteins. In cases of intensive hyperfunction, especially in its early stage, the activation may be insufficient, which leads to disturbance in the structure and metabolism

of the myocardium. Finally all this considerably disturbs the contractility of the myocardium and conduces to the development of heart failure.

In the treatment of the chronic heart failure syndrome an important role is played by diuretics, saluretics in particular. Hypothiazide must be mentioned in the first place. The substance is fairly well known and is extensively used in treating heart failure. The diuretic effect of hypothiazide is associated with its action on the enzymes of the proximal tubules, which participate in the transport of sodium, and, to a lesser extent, with the blocking of carboanhydrase of the distal tubules, which effect the process of H_2CO_3 and H-ion formation. As a result re-absorption of sodium decreases and the elimination of sodium and water increases. However, when hypothiazide is used potassium is eliminated in addition to sodium. The action of hypothiazide is largely individual. Its doses vary between 25 and 100 mg. We usually administer it in a dose of 50 mg every third day. Its administration requires caution in connection with the danger of the developing hypotension. The second negative property of hypothiazide is the increased excretion of potassium, which must be particularly taken into account in myocardial infarction in which the electrolyte balance, metabolism of potassium in particular, is disturbed. This disturbance may lead, for example, to arrhythmias. As Vinogradov and Matveev point out, prolonged administration of hypothiazide may cause even irreversible changes in the kidneys. Treatment with hypothiazide must therefore be simultaneously accompanied with administration of potassium either with the diet, for which purpose dried apricots, raisins and baked potatoes rich in potassium salts are included in the daily food, or through its administration in the form of potassium chloride or potassium acetate per os in a dose of 20 ml of a 10 per cent solution 2-3 times a day.

A milder side effect is produced by diacarb (acetazolamide) whose diuretic effect is connected with a depression of carboanhydrase at the level of the renal tubules and connected with this depression of reabsorption of H^+ -ions. Diacarb increases kaliuresis to a much lesser extent than does hypothiazide and usually does not decrease arterial pressure. There are various schemes of administering diacarb. Some authors recommend decreasing doses of the substances. According to their scheme, diacarb is administered in a dose of 0.5 g three times a day on the first day, twice on the second day and once on the third day. Like Votchall (1963), we also administer diacarb in a dose of 0.5 g twice a day with an interval of 1-2 hours. It should be noted that the diuretic effect of diacarb is weaker than that of hypothiazide.

As we have already pointed out, a new diuretic lasix, which also belongs to sulphanilamide derivatives, has of late been successfully used. The diuretic effect of lasix is superior to that of other diuretics. It is important that by increasing renal filtration and contri-

buting to excretion of sodium it does not cause any significant elimination of potassium from the tissues and hypokalaemia. For example, according to Klinfelder (1963), in a dose of 25-30 mg lasix increases the elimination of potassium only 20-25 mEq/l in 24 hours, whereas elimination of sodium reaches 75 mEq/l. About the same data are reported by Soviet authors. We usually administered 40-80 mg of lasix per os at intervals of 3-4 days and noted, like the other authors (Stokes, 1964, and Kiessling, 1965), a diuretic effect in nearly 90 per cent of cases of chronic heart failure. Despite the fact that the use of lasix only slightly affects the content of potassium in the blood and tissues we usually administer various potassium preparations in order to exclude even the slight possibility of disturbing the electrolyte balance.

The quest for saluretics possessing more potent diuretic properties, on the one hand, and devoid of negative influence on the electrolyte balance, the potassium metabolism in particular, on the other hand, is under way. In connection with this, we may mention triamterene (dytac, dyrenium), a British preparation, and ademin, a closely related Soviet preparation. Triamterene, which is usually administered in a dose of 100 mg after meals twice a day for a period of 5-7 days, possesses marked diuretic action, which is not inferior to that of lasix; at the same time it not only does not increase the excretion of potassium, but even somewhat decreases it (Baba *et al.*, 1962; Anichini *et al.*, 1963; Turner and Sowry, 1964, and Sidorenko, 1966). In the character of its action ademin resembles triamterene, although it possesses less diuretic properties. It is usually administered in a daily dose of 150-250 mg.

The development of myocardial infarction is usually accompanied with an increase in the content of aldosterone in the blood. Regarding this reaction as adaptive and protective, aimed at preserving the vascular tone, we emphasized the possible disturbance in aldosterone metabolism and in connection with it in the electrolyte metabolism attended with retention of water. Although the possibility of using aldosterone antagonists in heart failure (aldactone, spironelactone) is being discussed (Tublin and Berman, 1960; Bayley *et al.*, 1962; Kukes, 1963; Kononyachenko and Gerasimova, 1964 and A. V. Vinogradov and Sycheva, 1967), the question of their administration in myocardial infarction remains open. We did not observe any significant results on using aldactone in cases of heart failure associated with myocardial infarction. Much more promising is suggestion of using a mixture of diuretics (A. V. Vinogradov *et al.*, 1969). For example, addition of triamterene to hypothiazide in a 2.0 : 1,5 proportion appreciably reduced the loss of potassium, and a mixture of equal parts of these substances, while increasing the secretion of urina and sodium, completely prevented the exhaustion of the potassium reserves of the organism. According to A. V. Vinogradov *et al.* (1969), a mixture of hypothiazide, aldactone and ademin in a 1 : 1 : 1.5 ratio proved to be a potent

inhibitor of the mechanism of cation metabolism. In their opinion, a mixture of lasix, aldactone and triamterene is the most potent diuretic which at the same time does not disturb the potassium metabolism.

Myocardial infarction is usually accompanied with a decrease in myocardial contractility which in some cases persists even after formation of the scar. This gives rise to the question of the necessity of prolonged administration of digitalis or related substances (lantoside, digitoxin, isolanid) in order to treat chronic heart failure that aggravates in such cases the course of myocardial infarction. Many aspects of this problem have of late been reconsidered.

We have mentioned above the influence of cardiac glycosides on the course of chronic heart failure. Today physicians are no longer afraid to administer these preparations for a long time, even months, if necessary, or even to discharge the patients from the hospital with a recommendation to continue the treatment as out-patients. We are against using digitalis and the related substances indiscriminately, without due regard for the organism's individual properties, without a study of the reaction to their administration in particular. However, more extensive use of digitalis preparations in heart failure associated with myocardial infarction undoubtedly improves the prognosis in this severe complication.

Digitalis is being used much more seldom and is replaced by more purified preparations—isolanid, digoxin, digitoxin. It is difficult to recommend doses of these preparations. Not a single method of treatment requires such individualization as that with cardiac glycosides, especially in myocardial infarction. In our opinion two main factors must be considered, i.e. the state of coronary circulation after the appearance of myocardial infarction (frequent attacks of angina pectoris and their increase on administration of digitalis) and heightened excitability of the myocardium manifested during treatment of various rhythm disturbances with digitalis.

The findings of our co-worker Goldberg (1968) based on long, automatic, continuous watching of the ECG show that on administration of digitalis preparations transient disturbances in rhythm often arise (in 7 of 23 patients) and may subsequently become the source of graver complications, including ventricular fibrillation. In using digitalis preparations it is therefore necessary to exercise thorough and frequent control of the patient's pulse and the ECG. Simultaneous administration of potassium, co-carboxylase, vitamins B_1 and B_6 and other substances is expedient. Despite a series of studies (Votchal, 1963; Malmcrona *et al.*, 1966 and other authors) indicating the absence of a negative effect of cardiac glycosides on coronary circulation, we usually administer these substances on a background of therapy with vasodilators and anticoagulants.

9

TREATMENT IN THE PERIOD OF REHABILITATION

Physicians experience considerable difficulties in determining the periods of the course of myocardial infarction. As it seems to us, it is possible to distinguish more or less definitely the acute period the distinctive feature of which, from the standpoint of treatment, is the use of substances, which prevent and limit the development of the focus of necrosis and the appearance of some complications or are aimed at treating already developed complications. However, there are also some difficulties here. If, for example, we were to determine the acute period from the morphological point of view, this might be the period of formation and demarcation of necrosis and that of consolidation of myocardial infarction, depending on which this period will last either days or weeks. Still greater difficulties exist in determining the period of rehabilitation. It should be noted that it actually begins on the first days of the disease and does not end even on discharge from the hospital.

Thus there is a close relation between the periods we distinguish, which are largely conditional and mainly depend on the peculiarities of the clinical course of the disease. The conception of the close interrelation between the periods is important from the standpoint of the succession of the various methods of treatment.

Elaboration of the methods of rehabilitation therapy in myocardial infarction is of late becoming much more important. The main principle of rehabilitation is a maximum restoration of functions of various organs and systems disturbed in connection with myocardial infarction in order to ensure the physical activity and working capacity of these patients. Not only medicamentous therapy, but also a number of psychological, physiotherapeutic, sana-

torium, spa and other factors play an important role in solving this problem.

Rehabilitation treatment appeared when the Soviet health services were just coming into being. In its essence and principle the Soviet system of medical service has the best prerequisites for rehabilitation therapy. Free treatment, close connection between polyclinic and hospital treatment, organization of a wide network of sanatoria, and social insurance form the material base which accounts for the successes of rehabilitation therapy. Attemps at elaborating the principles of rehabilitation therapy in myocardial infarction and at distinguishing the stages of this process can be found as early as the studies of G. F. Lang. But despite the fact that our country has all the material prerequisites for most effective rehabilitation and several studies dealing with various aspects of this problem have been carried out, we are just beginning to substantiate scientifically the system of rehabilitation therapy in myocardial infarction in all stages of the treatment.

There is certain controversy in determining the stages of rehabilitation. Some authors hold that it must begin in the period when the patient is discharged from the hospital. From our point of view this is a fundamentally wrong, scientifically unsubstantiated approach to the system of rehabilitation therapy. It must begin in the first days of the disease. As a matter of fact, does not restoration of working capacity depend on how fast the complications of myocardial infarction will be eliminated? Suffice it to point out that the use of fibrinolytic enzymes and heparin resulted in an 80 per cent decrease in the incidence of thromboembolic complications. The use of cardiac glycosides at the early periods of the disease decreases the incidence of heart failure 50 per cent. Moreover, even such a factor, seemingly so distant from rehabilitation, as the period of hospitalization of myocardial infarction patients, also influences the duration of their sick-leave. According to the data obtained in Kishinev, when the patients were admitted on the first day of the disease, their stay in hospital was an average 64 days, whereas, when hospitalized after two weeks of the disease, it was 90 days from the moment of admittance. It follows that the scheme of rehabilitation therapy must be elaborated on the very first days of the disease considering the course of myocardial infarction.

The organization of system of rehabilitation envisages primarily a strict succession of measures in various stages of rehabilitation. It is necessary to proceed from the physiological prerequisites, peculiarities of the pathological process and the compensatory potentialities of the organism.

To begin with, it is necessary to distinguish the hospital and after-hospital stages of rehabilitation. This is largely a division according to the organizational principle. From the standpoint of the peculiarities of the pathological process and the evaluation of the compensatory potentialities the rehabilitation must be divided

into three periods, i.e. stabilization, mobilization and reactivation.

The first period coincides with that of consolidation of myocardial infarction, belongs entirely to the stage of hospital rehabilitation, and, from the medical point of view, is manifested in a striving to foster the quickest possible cicatrization, disappearance of the symptoms of the disease and prevention of complications. It is precisely in this stage that the treatment and prevention of heart failure, arrhythmias, etc., begin. Complete and adequate treatment carried out in the acute period ensures rapid restoration of the organism's functions.

The period of mobilization begins in the stage of hospital rehabilitation and continues under conditions of sanatorium and polyclinical observation. Its main task is adequate evaluation of the organism's functional state and measures aimed at its normalization. It is precisely this stage that now requires attention and correct evaluation. Unfortunately, there are considerable difficulties. To begin with it is difficult objectively to evaluate the state of the different systems. The myocardial contractility and the compensatory potentialities of coronary circulation are now evaluated somewhat better (telecardiography, examination of the phasic structure of the cardiac cycle and the minute volume of the heart), whereas the problems of psychological rehabilitation, the influences of neuro-emotional factors on coronary circulation, and the compensatory regional circulation have not been sufficiently studied yet. Too little attention is being devoted in the system of rehabilitation measures to evaluating external breathing, an important index of the organism's compensatory potentialities. All these problems play an important role in evaluating the patient's working capacity.

In speaking of psychological factors it is necessary to note that nearly 80 per cent of myocardial infarction patients exhibit considerable psycho-emotional changes. A thorough evaluation reveals reactions of emotional immaturity in 70 per cent of patients, signs of considerable psychic stress in 80 per cent and a sense of fear in 84 per cent. We think of anticoagulative therapy, anti-arrhythmic agents etc., but seldom dwell on the psychological essence of the process and hardly ever resort to psychotherapy.

It is important to study coronary circulation not only after a physical exertion, but also after emotional and psychic loads. It has turned out that they can cause negative changes in the ECG of a number of patients in the form of a depression in the *S-T* interval, inversion of the *T* waves, and rhythm disturbances. The first experience in the field of psychological rehabilitation indicates that with properly organized psychotherapy the patients' occupational possibilities are more quickly restored.

Whereas the method of medicamentous rehabilitation was in the foreground in hospitals, in sanatoria and polyclinics the method

of physical and psychological rehabilitation, the elements of which were formed in the hospital, begins to prevail. It is difficult to overestimate the importance of the sanatorium stage. Correctly organized sanatorium treatment plays a most important role in restoring the working capacity of myocardial infarction patients. According to the data of some authors, in 60 per cent of patients treated in sanatoria the positive effect persisted over a period of one year and 70 per cent returned to their former occupations. According to the Institute of Cardiology, sanatorium treatment produces a positive effect on coronary circulation.

The period of mobilization ends in the polyclinic where the organism's functional potentialities are finally determined and recommendations concerning the occupation and future work are given. This is a most important stage that largely determines the patient's fate. Here, too, begins the period of prolonged and active observation of patients. A correctly determined psychological and physical preparation of the patient for a return to work, and an optimum maintenance medicamentous therapy enable the patient to preserve not only his health, but also working capacity for a long time.

Finally, the period of reactivation is directly connected with the patient's return to his occupation activity. In this period the psychological and social problems come to the foreground. In the preceding periods the organism's functions were restored, a maximum compensation was achieved and the psychological prerequisites for the patient's return to work were created. In the third period the physician, psychologist and sociologist, who must in a large measure be physician of the Medical Control Commission and the Medical Expert Commission for Evaluation of Working Capacity, and a trade-union physician determine whether or not the patient may work at his former job, or recommend a new occupation.

Most authors (Fogelson, Khvilivitskaya, and others) justly point out that occupational activity, which corresponds to the heart condition, not only stimulates the course of the restorative processes, but also accelerates the re-adaptation to physical and emotional loads.

Having compared two groups of patients of the same age and with a similar course of myocardial infarction Kulikova has shown that in persons continuing their work pathological changes in the ECG and the phasic structure of the cardiac cycle appear less frequently and are less strongly pronounced.

The question of the working capacity of patients who have survived myocardial infarction is very complicated. It is still unclear whether it is best to exclude the patient from the work which constitutes part of his life as a member of society or to retain him in the sphere of his former activity and thereby to prevent psychoemotional and 'stress' conditions.

Indirect-action Anticoagulants

Most of the therapeutical methods employed in the period of rehabilitation are a direct continuation of the treatment which was begun in the acute period. For example, the treatment with vasodilatating agents is often continued in the period of rehabilitation, while therapy with indirect-action anticoagulants is a logical continuation of the treatment with fibrinolytic substances and heparin administered in the acute period. The peculiarities of the blood thrombogenic properties in myocardial infarction, and the local changes in the coronary vessels and heart cavities, create a danger of thrombus formation and the appearance of thromboembolic complications in the more remote periods after myocardial infarction. As our studies and those of our co-workers (Nikolaeva, 1962, and Mazur, 1966) have shown, activation of the anticoagulation system is observed in the first days of myocardial infarction, which may be regarded as a manifestation of a peculiar protective reaction. The increase in fibrinolytic activity and in the content of heparin persists only during the first days; subsequently they return to the normal level. Conditions for the appearance of recurrent thromboses and thromboembolic complications may arise because the activity of the coagulative factors remains on the former level.

The physicians therefore are faced with the task of reducing the activity of the blood coagulation system and thereby relatively to enhance the activity of the anticoagulation mechanisms. Today we can do this by using indirect-action anticoagulants. Despite the fact that the history of employing indirect-action anticoagulants already numbers several decades the discussion of their effectiveness and expedience is still under way. However, with years fewer and fewer opponents of this therapy remain. The results of numerous observations not only on the transient, but also prolonged (over a period of several years) administration of indirect-action anticoagulants enable most authors to recommend their use in myocardial infarction. Leading Soviet cardiologists (Myasnikov, Lukomsky, and others) and also eminent foreign clinicians (Wright, White, Owren, Deutsh, Frowent, Perlik) point out a considerably improved prognosis of myocardial infarction on prolonged use of anticoagulants.

Administration of indirect-action anticoagulants has made it possible first of all to reduce the incidence of recurrent myocardial infarctions and thromboembolic complications (Kushelevsky, 1958; Shestakov, 1962; Raevskaya, 1964, and Chazov, 1970). According to Lukomsky and Kazmina (1967), the use of anticoagulants has resulted in a decreased incidence of thromboembolic complications (from 19.5 to 5.6 per cent). Shestakov points out that wide use of anticoagulants has decreased mortality from myocardial infarction to 8.5 per cent. According to Royston (1967), of the 318 patients treated with anticoagulants 83 per cent were alive after five years,

whereas among the untreated patients only 50 per cent survived. Wessler and Gaston (1966) hold that owing to the use of anticoagulants in myocardial infarction the mortality was reduced by 3-4 per cent.

Griffith *et al.* (1962) report that anticoagulation therapy made it possible to reduce mortality from 54 to 22 per cent. Hess (1967) holds that prophylactic administration of anticoagulants prevents about 50 per cent of myocardial infarctions. The data of a number of other Soviet and foreign authors concerning the effectiveness of treatment with indirect-action coagulants could be cited, but this method is now so widely used that, in our opinion, there is no need proving it once more.

However, in speaking of the tendencies of the therapy with anticoagulants we must first point out the striving for a differentiated approach to their administration depending on the extent of the infarction, its complications, the patients' age and other concomitant factors. In cases of myocardial infarction it is risky to derive mean figures which often do not reflect the peculiarities of the course of the disease and the therapy. For example, according to Konyaev *et al.* (1964), anticoagulation therapy did not considerably affect the prognosis in cases of extensive necrotic changes in the myocardium, but improved the course of the pathological process in elderly patients and on the appearance of signs of heart failure. It seems to us that in evaluating the possibilities of this method it is, first of all, necessary to take into account the peculiarities of the course of myocardial infarction.

The second tendency consists in a search for, and utilization of, indirect-action anticoagulants devoid of toxic and side effects, but at the same time possessing marked anticoagulation action. It is precisely this factor that can explain that a number of Soviet preparations, i.e. omephin, diphenacine, napharine, etc., have appeared only of late.

In recent years the conceptions of the mechanism of action of indirect-action anticoagulants have broadened. Their effect is due not only to the depression of the prothrombinogenic function of the liver, but also to a decreased production of a number of coagulation factors—V, VII, and others. Determination of the optimum therapeutic level of blood prothrombin is the most complicated and moot question. From the experimental findings, e.g. of Kudryashov *et al.* (1964), it follows that thrombogenesis may be totally prevented by reducing prothrombin to 10 per cent. But this critical figure cannot be accepted in the clinic because of the danger of severe haemorrhagic complications. In connection with this it is clear why thromboses develop even in cases of treatment with anticoagulants. However, we are not inclined to ascribe thromboembolic complications only to the changes in biochemical factors. Local morphological disturbances in the vascular wall, and local changes in the content of enzymes participating in blood coagulation, also play

an important role. Unfortunately, the local factors have of late begun to be studied much less, although their role in the pathogenesis of thrombosis, in our opinion, is sufficiently important. It seems to us that in the mechanisms of thrombogenesis on a background of anticoagulation therapy it is necessary to take into account not only the general changes, in particular in the system of blood coagulation, but also the local disturbances in the vessels. This is the more substantiated, since thromboembolic complications have been described even on a background of haemorrhagic complications provoked by anticoagulation therapy.

Most authors hold that for effective therapy it is necessary to prolong the prothrombin time 100-150 per cent compared with the norm and bring the prothrombin index to 30-50 per cent (Wright *et al.*, 1954; Lapin, 1955; Kushelevsky, 1958; Lukomsky and Kazmina, 1961; Deutsch, 1962, and Perlik, 1964). This is also our point of view.

There are various schemes of using anticoagulants. Their administration, like any other treatment of myocardial infarction, requires, in the first place, an individual approach. This is, in particular, manifested in a choice of the optimum dose of the substance. We especially emphasize the significance of such a dose. It makes it possible not only to choose the most effective and expedient method of treatment, but also to establish the intolerance for the anticoagulant. According to our observations, a sharp decrease in blood prothrombin on using a minimum dose is characteristic of patients predisposed not only to haemorrhagic complications, but also (on prolonged administration) to marked changes in the liver.

The duration of the use of anticoagulants is a very complicated question. Indirect-action anticoagulants must be used during the months immediately following the myocardial infarction, at least in the hospital. Today they are much more widely used in the Soviet Union by out-patients over a period of many years (Lukomsky and Kazmina, 1961; Lukomsky, 1964; Boev, 1967; Chazov, 1970, and others). Our co-workers, Ananchenko and Dolbilova, specially studied the role of anticoagulative therapy in the complex of methods of treating out-patients who had survived myocardial infarction. Of the 100 patients given this substances over a period of three years only one had a recurrent myocardial infarction and not one of the patients died. A number of authors report continuous administration of indirect-action anticoagulants over a period of two or three years with good results. There are reports on successful administration of indirect-action anticoagulants for eight or ten years, although the contingent of patients was extremely limited (Wright, Perlik, and other authors). It should be emphasized that the organizational principle of rendering aid to patients who have survived myocardial infarction in the Soviet Union creates the conditions for safer, more effective and extensive use of anticoagulants.

The question of the duration of using anticoagulants after myocardial infarction requires further investigation and, what is the most

important, accumulation of extensive factual material with well-organized control. However, we should like already now to state our point of view on the so-called method of intermittent therapy suggested by some authors. As observations conducted in our clinic by Nikolaeva show, frequent administration, and especially discontinuation of anticoagulants, are conducive to considerable fluctuations in the blood thrombogenic properties and create a danger of thrombus formation. Rapid and frequent discontinuation of anticoagulants may sharply increase the concentration of the coagulation factors and with an inadequate reaction of the anticoagulation system lead to the formation of a thrombus. These fluctuations are particularly dangerous during the first two or three months after the onset of infarction. The optimum dose, while retaining the prothrombin index of 40-50 per cent, makes it possible, as a rule, to avoid haemorrhagic complications and discontinuation of the preparation. It is necessary to emphasize the importance of thorough laboratory control, especially during the first month following the development of myocardial infarction.

Previously physicians could use only dicoumarin (dicoumarol) and, at best, neodicumarin (ethyl biscoumacetate). Today we have a complex of indirect-action anticoagulants which enable us to make a differentiated approach to their administration. For example, phenyllin (phenindione) acts more rapidly than diphenacine and pelentan (ethyl biscoumacetate) more strongly and rapidly than nafarin (phenprocoumon). In compiling the scheme of treatment due regard for these peculiarities makes it possible to avoid possible complications in the course of treatment and obtain more effective results.

The best known preparation used today is neodicumarin. It is one of the coumarin preparations, is largely devoid of toxic properties and acts quite rapidly. Its effect may be observed already 16-18 hours after its administration. Initially the usual dose of the preparation is 0.2 g 3 times a day, the maintenance dose is 0.1 g 1-2 times a day. Of its peculiarities mention should be made of the considerable and fairly rapid fluctuations in the blood prothrombin content on changing the dose. They are less strongly pronounced than in the treatment with pelentan, another anticoagulant. Pelentan, which is an oxycoumarin derivative, causes a rapid inhibition of the production of factors VII and X and of prothrombin. It is rapidly eliminated from the organism, which makes it necessary to take it more frequently than the other anticoagulants. If we take into account that to produce an effect fairly large doses are needed (0.3 g 3 times a day), it becomes clear why it is difficult to regulate the blood prothrombin level and therapy with this preparation. A quest for preparations, which might cause a more gradual, but more stable depression of the prothrombinogenic function, is therefore now under way. Four new preparations, i.e. phenyllin, diphenacine, omephine and nafarin, are now the most widely used in the clinic.

Phenyllin belongs to the indandione group. On administration of phenyllin the maximum effect occurs in 36 hours. It is usually eliminated in 40-48 hours. It is administered in a dose of 0.03 g 3-4 times a day with a subsequent maintenance dose of 0.03 g 1-2 times a day. Diphenacine, which acts more slowly than phenyllin belongs to the same group (Kazmina), but produces a more stable effect. Its maximum effect occurs in two days. The daily dose is 10 mg, the maintenance dose 5 mg. The third preparation of this group is omephine, which is usually administered during the first days of the treatment in doses of 100-200 mg with a gradual decrease to 50-100 mg a day. Sharp fluctuations in the prothrombin level are hardly observed on using this substance. The usual state of the coagulative system after the preparation is discontinued is the most rapidly restored on administration of neodicumarin and the most slowly under the action of diphenacine.

Nafarin, suggested by Lakin, has of late begun to be successfully used in the clinic. Producing a milder, but at the same time sufficiently stable anticoagulative effect, it is more widely used (Lukomsky and Kazmina, 1968; Chazov *et al.*, 1969, and others). We usually conduct the treatment according to the following scheme: after a test dose of 10 mg we administer 50-60 mg on the first day. If on the second day the level of prothrombin decreases less than 20 per cent of the initial, we reduce the dose to only 35-40 mg a day, whereas if it decreases to the therapeutic level we begin to administer the maintenance dose of 10 mg.

Reports have now appeared (Lukomsky *et al.*, 1967) on administration of another anticoagulant related to nafarin, i. e. nitronafarin. Possessing marked anticoagulative properties the preparation decreases the activity of factors II, VII, IX and X and produces a stable effect (72-96 hours). It is administered in a dose of 20-30 mg, which is reduced to the maintenance level of 2.5-10 mg on the fourth or fifth day of treatment.

In conclusion it should be emphasized that an individual approach to each patient is one of the main prerequisites for successful anticoagulative therapy. This makes it possible not only to create an optimum therapeutic regimen, but also to avoid possible complications, in the first place the haemorrhagic ones, the appearance of which can be prevented by a careful analysis of the dynamics of the blood prothrombin content and by periodical examinations of the urine. As a rule, discontinuation of the anticoagulant leads to disappearance of the haemorrhagic phenomena. Vikasol (menadione sodium bisulphite) may be administered in grave cases. As we have already pointed out, indirect-action anticoagulants may cause changes in the liver. Liver diseases in the patient's anamnesis must therefore always put the physician on guard. Of the other contra-indications mention may be made of ulcers, nephritis, sepsis, and severe allergy. It should be emphasized that indirect-action coagulants may also provoke allergic reactions.

'Coronary' Agents

The question of using coronary agents in myocardial infarction is still debatable and barely studied. Most of the American and British authors working on the problem of myocardial infarction do not use these agents for its treatment. In Soviet cardiology, too, there are few such purposeful studies carried out on a sufficiently high scientific level and with good control. The problem of effective use of 'coronary' agents deserves greater attention. From the pathogenic point of view this is accounted for by several factors. There is on opinion that in myocardial infarction coronary spasm occurs not only in the region of the focus of affection, but also in the paranecrotic zone and even in distal parts of the heart. It should be emphasized that the focus of necrosis becomes the source of pathological impulses which may be conducive to the spasm of the cardiac arteries. To eliminate this reflex spasm means to reduce ischaemia of the myocardium and improve the course of the pathological process. The second factor that should be taken into consideration is the biochemical changes in the myocardium connected with the formation of the focus of necrosis (acidosis, etc.) which create prerequisites for deterioration of coronary circulation. Finally, one of the causes of the development of myocardial infarction is coronary atherosclerosis, which is fraught with the possibility of recurrent disturbances in coronary circulation. This accounts for the necessity of administering 'coronary' agents in myocardial infarction and the search for the most effective ways of improving coronary circulation.

Today we have a number of 'coronary' agents with various mechanisms of action and different points of application. They may be divided into substances, the 'coronary' effect of which is due to the spasmolytic action mainly through the nervous system (papaverine, no-spa [drotaverine], etc.), substances which influence the function of the heart's adrenergic receptors (inderal [propranolol], the blocking agent of the β-adrenergic receptors) and substances whose effect is due to the change in the metabolic processes in the myocardium (corontin [prenylamine], persantin [dipyridamole], etc.). The effectiveness of all these preparations continues to be debatable even under conditions of chronic coronary failure. Its potentialities in myocardial infarction are particularly unclear since there are many contributory factors which render the evaluation of the action of 'coronary' agents difficult. It should be kept in mind that the findings of experimental, pharmacological studies do not always coincide with the clinical effect of the preparation in question. For example, the experiment with using such substances as intensain (carbocromen), etc., show not only the improvement of coronary circulation, but also an opening of the collateral network and even its development. However, there is no authentic confirmation of the significant effect of the substances on the course of the main patho-

logical process. The most that can be noted on their administration is the prevention of angina pectoris attacks. Nevertheless, the prophylactic action of 'coronary' agents is of a considerable importance to the prognosis in myocardial infarction patients. Their direct coronary dilatative effect cannot be completely denied, especially since the improvement of coronary circulation on their administration has been shown in a number of clinical studies. The studies were carried out not only by the method of determining the coronary blood flow by the radioactive krypton contested by some authors, but also by the direct catheterization of the coronary sinus (Votchal and Vysoky, 1966; Ito *et al.*, 1966, and Doshchitsyn *et al.*, 1967). For example, comparing the action of a number of 'coronary' agents, Ito *et al.* (1966) discovered a marked increase in coronary circulation in cases where persantin (dipyridamole) and theophylline (theocin) derivatives were used and did not find such an action on using papaverine. At the same time the oxygen deficit in the myocardium increased on administration of theophylline derivatives. This fact also emphasized by Raiskina necessitates cautious administration of euphylline (aminophylline) during the acute period of myocardial infarction. Euphylline increases the oxygen requirements of the myocardium, enhances the excitability and is often conducive for extrasystole. In our opinion, all this makes it scarcely fit for administration as a 'coronary' agent in myocardial infarction.

On the basis of objective studies Votchal, unlike Ito, points out a distinct coronary dilatative effect of papaverine.

Papaverine is widely known as an antispasmodic, whose vasodilatative effect is based on a decrease in the tone of the smooth muscles in the vascular wall (Anichkov and Belenky, 1955). Administration of papaverine undoubtedly prevents coronary spasm, especially of a reflex origin, and may improve coronary circulation. Like most clinicians (V. N. Vinogradov, Myasnikov, Votchal), we consider it expedient to administer large doses of papaverine. Usually we prescribe it in a dose of 0.06 g 3 times a day. Only such doses can produce the needed coronary dilatative effect. In 1961 Hungarian pharmacologists developed a new spasmolytic agent—no-spa (drotaverine), which is, like papaverine, an isoquinoline derivative, but possesses weaker vasodilatative properties. Today it is widely used, in myocardial infarction in particular (Kozhevnikov, 1963, and Kokosov and Heinonen, 1966). It is absorbed in the gastro-intestinal tract much more rapidly than papaverine, possesses more prolonged action and is devoid of any side effects. We therefore successfully administered it not only intramuscularly as a solution in a dose of 20-40 mg 2-3 times a day, but also perorally in a dose of 40-80 mg 3 times a day. Statements have of late appeared to the effect that the coronary dilatative effect of no-spa is exaggerated and that control studies (using the double blind method) revealed a small percentage of positive results compared with the control

(Myasnikov *et al.*, 1968). We can agree that the effect of many 'coronary' substances was better for psychological reasons when they were studied clinically and were not widely available. This once more emphasizes the need of careful objective evaluation of their action. On the other hand we must take into consideration the variety of mechanisms accounting for the appearance of coronary failure, which requires administration of various agents with different mechanisms of action on the pathological process. If the no-spa or papaverine is ineffective, it does not mean that we must not try to treat the patients with corontin (prenylamine) or persantin (dipyridamole), although, for example, in a large percentage of cases corontin may also prove ineffective (Myasnikov *et al.*, 1968). At the same time many authors positively evaluate the action of the Hungarian preparation (Kertesi, 1957; Votchal and Vysotsky, 1966, and other authors). It is possible that the differences of opinion are dependent on the various methods of administering the preparation. Whereas Myasnikov and his associates administered it in a dose of 15-30 mg 3 times a day, Kertesi, who considers that corontin accelerates the coronary blood flow and conduces to the opening of the collateral vessels, used much larger doses, i.e. 60-120 mg 3 times a day, and did not observe any signs of toxic action of the preparation. However, it must be pointed out that corontin is poorly tolerated by patients with disturbances in intraventricular conduction.

In addition to the foregoing preparations now fairly widely used, a number of new 'coronary' agents, whose effect is due to the influence on metabolism in the myocardium, have appeared. For example, persantin, closely related to corontin in the character of its action, proved effective in 75 per cent of patients given a dose of 75 mg 3 times a day (Messerich, 1966). Similar data are cited by Kipshidze and Tripdiani (1963). Blocking agents of β-adrenergic receptors have of late been successfully used as a 'coronary' preparation. The most widely known of these substances is inderal (propranolol). Despite the fact that the preparation possesses a marked capacity for decreasing the incidence of angina pectoris attacks we refrain from administering it in myocardial infarction. The positive effect of inderal is connected not with an increase in the coronary blood flow, which may even decrease, but with a decrease in the oxygen requirement of the myocardium. But considering that the preparation reduces the contractility of the myocardium (Fleming and Hamer, 1967, and Shkhvatsabaya *et al.*, 1967) and in some cases causes the development of circulatory failure (Shapiro *et al.*, 1965) our negative attitude to the administration of inderal in myocardial infarction becomes understandable.

Isoptin (verapamil) and intensain (carbocromen), new and, according to some findings (Doshchitsyn *et al.*, 1967, and Myasnikov *et al.*, 1968) very effective preparations, have as yet been insufficiently studied, especially as regards their use in myocardial infarction. They affect the contractility of the myocardium much less

than does inderal and at the same time enhance coronary circulation. Isoptin is administered in a dose of 40 mg 3 times a day, and intensain—150 mg 3 times a day. It is also necessary to dwell on long-action nitrates, i.e. nitropenton (pentaerythrityl tetranitrate) and nitrosorbid, as well as chloracizin. Our ideas of using chloracizin in myocardial infarction have gone through the same evolution as those of administering other preparations, i.e. at first it seemed very effective, but later its action was evaluated with greater reserve. According to Vikhlyaev, chloracizin possesses marked spasmolytic and cholynolytic properties. An interesting peculiarity of its action is its marked capacity for decreasing oxygen consumption of the heart (Kisin and Zubovskaya, 1964). According to some clinicians (Ostapchuk, 1960, and Tynyanova and Bernstein, 1966), chloracizin produces better results in coronary failure connected with coronary atherosclerosis than in angioneurotic and reflex disturbances in coronary circulation. It is administered in a dose of 0.015 g 3 times a day. The effect usually takes place in eight to ten days. Of the possible side effects mention should be made on xerostomia, decrease in appetite and occasionally vertigo. In our opinion, the preparation is inferior in effectiveness to the aforedescribed substances whose effects are due to their influence on the metabolism in the myocardium.

The use of nitric acid ethers, nitranol, erynit (nitropenton) and nitrosorbid was based on a striving to obtain the effect observed upon administration of nitroglycerin, but of longer duration. In our opinion, however, the change in the chemical structure resulted in a considerable decrease in the coronary dilatative properties of these preparations. Nitropenton is used the most extensively. Its effective dose varies very greatly and must be chosen individually (Votchal, 1963, and Gefter, 1967). The drug is usually administered in a dose of 1 tablet (10 mg) 3-4 times a day. It is considered that nitrosorbid is also effective in maximum permitted doses. According to Tviddiani and Dumbadze (1963), and Gefter (1967), the preparations of this group improve coronary circulation, which is objectively reflected not only in a decreased incidence of angina pectoris, but also in the changes in the ECG, ballistocardiogram and the phase analysis.

Some authors consider the preparations of this series less indicated in cases of angioneurotic forms of angina pectoris (Gefter, 1967). Today we cannot as yet recommend a more efficacious 'coronary' agent for myocardial infarction. The effect depends in each concrete case on the pathogenic features of the coronary failure. The most effective and universal preparation, in the sense of its action on the pathogenic mechanisms, is a subject of future research.

* * *

In describing the methods of treatment in the rehabilitation period of myocardial infarction we must not overlook the therapy of

the so-called postinfarctional syndrome, i.e. Dressler's syndrome. As was already pointed out, the leading role in the pathogenesis of this complication of myocardial infarction is played by auto-allergy connected with the appearance of antibodies to the antigen which forms in the focus of necrosis. Most authors (Raevskaya, 1964; Yurenev *et al.*, 1964, and Artemyev and Komarova, 1965) consider anti-allergic substances to be the most indicated during the postinfarctional syndrome. Prednisolone is usually used in a dose of 15-25 mg a day. Treatment of the postinfarctional syndrome with steroid substances improves the condition usually in the course of seven to ten days, i.e. the temperature falls, arthralgia and signs of polyserositis disappear, anaemia decreases, etc.; this must be remembered in differential diagnosis. In cases of disturbances in the water and salt metabolism, in the event of ulcers and a tendency toward an increase in arterial pressure, other anti-allergic substances may be resorted to, namely, antihistaminic preparations, salicylates and occasionally butadione.

Considering that no unimportant role in the appearance of the postinfarctional syndrome is played by the nervous system, i.e. the organism's reactivity, the combined therapy must include vitamin B_1 and B_6, ascorbic acid, ATP, etc. But the treatment of the postinfarctional syndrome must be individualized.

BIBLIOGRAPHY

Abrikosov, A. I. *Chastnaya patologicheskaya anatomiya. Serdtse i sosudy* (Special Pathological Anatomy. The Heart and Vessels). Moscow, 1947, Vol. 2, p. 82

Acheson, R. M. *Brit. J. Prev. Soc. Med.*, 1961, 15, 49

Adel, H. N., Daly, M. M., Deming, Q. B. *et al. Circulation*, 1962, 26, 681

Adlersberg, D., Zak, F. G. *J. Mount Sinai Hosp.*, 1952, 19, 289

Afanasieva, O. N., Mikhailova, N. A. *Materialy nauchno-prakticheskoi konferentsii vrachei 1-i bolnitsy* (Proceedings of the Scientific and Practical Conference of Physicians of the First Hospital). Moscow, 1967, 3

Afanasieva, O. N., Voshchanova, N. P. *Ter. arkh.*, 1965, 3, 67

Aflyatonov, F. S. *Rasprostranenie gipertonicheskoi bolezni i koronarnogo ateroskleroza i usloviya zhizni* (Distribution of the Hypertensive Vascular Disease and Coronary Atherosclerosis, and the Conditions of Life). Leningrad, 1964, 145

Agress, C. M. *Modern Trends in Disease of Coronary Arteries and Ishemic Heart Disease.* New York, 1964, 235

Agress, C. M., Binder, M. J. *Amer. Heart J.*, 1957, 54, 458

Ahn, B. von Ann. *N. Y. Acad. Sci.*, 1960, 90, 190

Akhunbaev, I. K., Frenkel, G. L. *Ocherki po shoku i kollapsu* (Papers on Shock and Collapse). Frunze, 1967

Albagli, Ch., Eshcar, J. *Brit. Heart J.*, 1963, 25, 536

Albrink, M. J. *Arch. Intern. Med.*, 1962, 109, 345

Aldinger, E. E. *Vasc. Dis.*, 1967, 4, 83

Alekseev, G. K. *Ter. arkh.*, 1959, 2, 60

Alekseev, S. G., Pushkareva, Y. Z. *Trudy Kubanskogo med. inst.* (Transactions of the Kuban Medical Institute). Krasnodar, 1956, 4, 51

Alekseev, V. P. Osobennosti Rasprostraneniya ateroskleroza u zhitelei g. Yakutska (Peculiarities of the Distribution of Atherosclerosis among the Inhabitants of the City of Yakutsk). Diss. Moscow, 1963

Allen, E. V., Barker, N., Hines, E. A. *Peripheral Vascular Diseases.* Philadelphia, 1955

Allison, R. B., Rodriquez, F. L., Higgins, E. A. *et al. Circulation*, 1963, 27, 170

Amelin, A. Z., Anshelevich, Y. V., Melzobs, M. Ya. *Arkh. pat.*, 1963, 1, 25
Amosov, N. M. *Vestn. khir.*, 1963, 4, 73
Andersen, K. L. *Exercise Physiology*, 1968, 193
Andreenko, G. V. In: *Lechenie antikoagulyantami i fibrinoliticheskimi sredstvami* (Treatment with Anticoagulants and Fibrinolytic Agents). Kaunas, 1967, 12
Andreenko, G. V., Chazov, E. I. In *Ateroskleroz i tromboz* (Atherosclerosis and Thrombosis). Moscow, 1964, 167
Andreichev, A. I. *Kardiol.*, 1963, 5, 33
Anichini, M., Gargano, N., Bartoralli, C. *Presse med.*, 1963, 71, 123
Anichkov, N. N. *Chastnaya patologicheskaya anatomiya.* T. 2. *Serdtse i sosudy* (Special Pathologic Anatomy. Vol. 2. The Heart and Vessels). Moscow, 1936
Anichkov, S. V., Belenky, M. L. *Uchebnik farmakologii* (Textbook of Pharmacology). Leningrad, 1955
Anichkov, N. N., Valter, A. V., Volkov, K. G. *et al. Trudy Vsesoyuzn. konf. patologoanatomov* (Transactions of the All Union Conference of Pathoanatomists). Moscow, 1956, 246
Anichkov, N. N., Volkova, K. G., Kakaion, E. E. *Pat. fiziol. i eksper. ter.*, 1957, 6, 3
Anokhin, P. K. *Fiziol. zh. SSSR*, 1957, 11, 1072
Anshelevich, Yu. V. Sravnitelnaya kharakteristika razlichnykh form koronarnoi nedostatochnosti (kliniko-biokhimicheskie i eksperimentalnye issledovaniya) (Comparative Characteristics of Various Forms of Coronary Failure. Cliniko-biochemical and Experimental Studies). Diss. Riga, 1966
Anttonen, V. M., Rautakoski, A. *Ann. med. intern. Fenn.*, 1956, 45, 183
Appelbaum, E., Nicolson, G. H. *Amer. Heart J.*, 1935, 10, 662
Ariev, M. Y. In *Koronarnaya nedostatochnost* (Coronary Failure). Moscow, 1949, 6
Ariev, M. Y. *Serdechnaya astma* (Cardiac Asthma). Leningrad, 1962
Ariev, M. Y., Vitushinsky, V. I., Rabinerzon, A. B. *Ter. arkh.*, 1935, 3, 67
Artemiev, Y. N., Komarova, Y. K. *Ter. arkh.*, 1965, 12, 78
Artusio, J. F. *Pharmacol. Exp. Ther.*, 1954, 111, 343
Askanas, L., Slidziewski, K., Rudnick, S. I. *et al. Seminar on Rehabilitation of Patients with Cardiovascular Diseases.* Warszawa, 1967
Askey, J. M., *Amer. J. Med.*, 1950, 9, 528
Aspenström, G. *Nord. Med.*, 1964, 52, 263-266
Astrup, T. *Wien. Z. inn. Med.*, 1958, 39, 373
Astrup, T. In *The Aetiology of Myocardial Infarction.* London, 1963, 603
Astrup, T., Albrechtsen, O. K., Claasen, M. *et al. Circulation Res.*, 1959, 7, 969
Auerbach, O., Hammond, E. C., Garfinkel, L. *New Engl. J. Med.*, 1965, 273, 775
Avdeev, M. I. In: *Voprosy sudebno-meditsinskoi ekspertizy* (Problems of Forensic Medicine). Leningrad, 1958, 186
Avtandilov, G. G., Kolenova, V. I., Ponomarenko, O. V. *Kardiologiya* (Cardiology). 1965, 1, 30
Baba, W. I., Tudhope, G. R., Wilson, G. M. *Brit. Med. J.*, 1962, 5307, 756
Bagdasarov, A. A., Alperin, P. M., Merkul, V. Y. *Ter. arkh.*, 1955, 5, 13
Baker, T. W., Willius, F. A. *Amer. J. Med. Sci.*, 1938, 196, 815
Bakulev, A. N., Saveliev, V. S., Savchuk, B. D., Belgov, V. Y. In *Nedostatochnost serdtsa i aritmii* (Cardiac Failure and Arrhythmias). Leningrad, 1966, 301
Bakumenko, M. S. *Ibid*, p. 342
Ball, D. *Amer. Heart J.*, 1938, 16, 203
Balotin, N. M. *Dis. Chest.*, 1959, 36, 86
Banta, H. D., Greenfield, J. C., Estes, E. H. *Amer. J. Cardiol.*, 1964, 14, 330
Barats, S. S. In: *Rasprostranenie gipertonicheskoi bolezni i koronarnogo ateroskleroza i usloviya zhizni* (Distribution of Hypertensive Vascular Disease and Coronary Atherosclerosis, and the Conditions of Life). Leningrad, 1964, 70

Barats, S. S. *Sbornik rabot Sverdlovskogo med. inst.* (Transactions of the Sverdlovsk Med. Inst.). Sverdlovsk, 1965, Book 45, 79
Barats, S. S., Volkov, V. S. *Materialy dokladov 7-go soveshchaniya po epidemiologii ishemicheskoi bolezni serdtsa, ateroskleroza i gipertonicheskoi bolezni* (Reports to the Seventh Conference on Epidemiology of the Ischaemic Heart Disease, Atherosclerosis and Hypertensive Vascular Disease). Moscow, 1969, 23
Barnes, A. R., *Amer. Heart J.*, 1934, 9, 734
Barnes, A. R., Ball, R. G. *Amer. J. Med. Sci.*, 1932, 183, 215
Barnes, A. R., Whitten, M. B. *Amer. Heart J.*, 1929, 5, 142
Barrie, H. J., Urback, P. G. *Canad. Med. Ass. J.*, 1957, 77, 100
Barry, A., Patten, B. M. In: *Pathology of the Heart.* Springfield, 1953, 87
Barta, I., Nagy, I. *Ztschz. ges. inn. Med.*, 1961, 1, 41
Bashour, F. A., Edmondson, R. E. *Circulation*, 1965, 32, Suppl. 2, 46
Baubine, A. V. Nekotorye voprosy epidemiologii infarkta miokarda v usloviyakh Litovskoi SSR (Some Problems of Epidemiology of Myocardial Infarction in the Lithuanian SSR). Diss. Kaunas, 1964
Baubine, A. V. In: *Rasprostranenie gipertonicheskoi bolezni i koronarnogo ateroskleroza i usloviya zhizni* (Distribution of the Hypertensive Vascular Disease and Coronary Atherosclerosis, and the Conditions of Life). Leningrad, 1964, 132
Baumgarten, W. *Amer. J. Physiol.*, 1899, 2, 243
Bayley, R. H. *Amer. Heart J.*, 1942, 24, 514
Bayley, R. H., La Due, J. S., York, D. J. *Amer. Heart J.*, 1944, 27, 657
Bayley, T. A., Forbath, P. G., Wilson, J. K. *et al. Canad. Med. Ass. J.*, 1962, 87, 1263
Bean, W. B. *Amer. Heart J.*, 1937, 14, 684
Bean, W. B. *Ann. Inter. Med.*, 1938, 12, 71
Beanlands, D. S., Gunton, R. W. *Amer. J. Cardiol.*, 1964, 14, 370
Bear, S., Heine, W. I., Krasnoff, S. O. *Amer. J. Med. Sci.*, 1951, 222, 500
Beligan, G., Molho, M., Sorin, E. *et al. Fiziol. norm. si pat.*, 1957, 4, 165
Belkin, V. S. *Ter. arkh.*, 1961, 12, 51
Belkin, V. S., Smetnev, A. S., Kovanov, V. V. *et al. Trudy 1-go Moskovskogo meditsinskogo instituta* (Transactions of the First Moscow Medical Institute). Moscow, 1965, 36, 297
Bellet, S. In W. Raab. *Prevention of Ischemic Heart Disease.* Springfield, 1966, 74
Bellet, S., West, J. W., Guzman, S. V. *Ann. N. Y. Acad. Sci.*, 1960, 90, 156
Bellet, S., West, J. W., Manzoli, U. C. *et al. Ann. N.Y. Acad. Sci.*, 1960, 90, 317
Bellet, S., West, J. W., Müller, O. F. *et al. Circulat. Res.*, 1962, 10, 27
Belli, C., Battistoni, L., Grigolato, V. *Minerva med.*, 1962, 53, 102
Belova, Z. M., Semenova, T. M. *Ter. arkh.*, 1966, 9, 89
Benda, L., Lujf, A., Moser, K. *Wien. Ztschz. inn. Med.*, 1966, 47, 421
Bender, A. D., Sullivan, F. J., Horwath, S. M. *Experientia*, 1963, 19, 254
Benson, E. S., Hallaway, B. E., Turbak, C. E. *Circulat. Res.*, 1958, 6, 122
Beresford, E. H., Earl., C. J. *Quart. J. Med.*, 1930, 23, 55
Berinskaya, A. N., Kalinina, N. V., Meerzon, T. I. *Iskhody i prognoz infarkta miokarda* (Results and Prognosis of Myocardial Infarction). Moscow, 1958
Berkowitz, D. *Coronary Heart Disease.* New York, 1963
Berkson, D. M., Stamler, J. *Wld.-Wide Abstr. Gen. Med.*, 1965, 8, 8
Berne, R. M., *Circulat. Res.*, 1958, 6, 644
Berne, R. M. *Physiol. Rev.*, 1964, 44, 1
Bierenbaum, M. L., Jacowitz, H., Fleischman, A. I. *Circulation*, 1965, Suppl. 2, 31/32, 11-3
Bing, R. J. *Amer. J. med.*, 1961, 30, 679
Bloch, J. H., Pierce, C. H., Manax, W. G. *et al. Surgery*, 1965, 58, 197
Blumgart, H. L. *Am. Heart J.*, 1939, 18, 600-603
Blumgart, H. L. *J.A.M.A.*, 1954, 154, 107
Blumgart, H. L. Schlesinger, M. J., Davis, D. *Amer. Heart J.*, 1940, 19, 1

Blumgart, H. L., Schlesinger, M. J., Zoll, P. M. *J.A.M.A.*, 1941, 116, 91
Blumgart, H. L., Zoll, P. M. *Circulation*, 1960, 22, 301
Blumgart, H. L., Zoll, P. M., Freedberg, A. S. *et al. Circulation*, 1950, 1, 10
Blumgart, H. L., Zoll, P. M., Wessler, S. *Trans. Ass. Amer. Physics.*, 1950, 63, 262
Bluzhas, I., Yankevichyute, U. *Materialy 15-i nauchnoi konferentsii prepodavatelei Kaunasskogo meditsinskogo instituta* (Proceedings of the 15th Scientific Conference of the Teaching Staff of the Kaunas Medical Institute). Kaunas, 1965, 16
Bockus, H. L. *Gastroenterology*. Philadelphia, 1966, V. 3
Boev, V. T. *Trudy 1-go Moskovskogo meditsinskogo instituta* (Transactions of the First Moscow Medical Institute). Moscow, 1967, 53, 189
Bogolepov, N. K. *Sov. vrach. sb.*, 1949, 13, 7
Bogolepov, N. K. *Klin. med.*, 1949, 3, 36
Bogolepov, N. K., Dubrovskaya, M. K. *Vrach. delo*, 1967, 1, 61
Bogolepov, N. K., Dubrovskaya, M. K., Ginzburg, E. M. *Vrach. delo*, 1967, 3, 41
Bogolepov, N. K., Erokhina, L. G. *Vrach. delo*, 1962, 12, 8
Bogolepov, N. K., Yurenev, P. N., Semenovich, N. I. *et al. Klin. med.*, 1966, 1, 37
Borhani, N. O., Hechter, H. H., Breslow, L. *J. Chron. Dis.*, 1963, 16, 1251
Botkin, S. P. *Kurs kliniki vnutrennikh boleznei i klinicheskie lektsii* (A Course in Clinical Aspects of Internal Diseases and Clinical Lectures). Moscow, 1950, 2, 467
Bouvrain, Y., Coumel, Ph., Saumont, R. *Cardiologia*, 1966, 49, 122
Boyer, N. H., Green, H. D. *Amer. Heart J.*, 1941, 21, 199
Brams, W. A., Gropper, A. *Illinois Med. J.*, 1940, 78, 246
Branwood, A. W., Montgomery, G. L. *Scot. Med. J.*, 1956, 1, 367
Braunwald, E. *Ann. Rev. Physiol.*, 1966, 28, 227
Bredt, H. *Beitr. path. Anat.*, 1949, 110, 100
Breneman, G. M., Drake, E. H. *Circulation*, 1962, 25, 862
Brereton, W. F., Sherlock, P., Cameron, D. J. *Arch. Intern. Med.*, 1965, 115, 311
Brikker, B. N., Volpert, Y. I. In: *Nedostatochnost serdtsa i aritmii* (Heart Failure and Arrhythmias). Leningrad, 1966, 209
Brown, R. G., Davidson, L. A., McKeown, T. *et al. Lancet*, 1957, 2, 1073
Brunner, D. K., Loebl, K., Altman, S. *Circulation*, 1962, 26, 693
Brunner, D. K., Manelis, G., Loebl, K. *Circulation*, 1962, 26, 692
Buchnem, F. S. P. van. *Acta Med. Scand.*, 1967, 181, 403
Büchner, F. *Die Koronarinsuffizienz*. Dresden, 1939
Büchner, F. *Handbuch der allgemeinen Pathologie*. Berlin, 1961, Bd. 5, T. 1
Burch, G. E., Horan, L. G., Ziskind, J. *et al. Circulation*, 1958, 18, 325
Burn, J. H. *Ann. N.Y. Acad. Sci.*, 1960, 90, 70
Burn, J. H. *Ann. N.Y. Acad. Sci.*, 1960, 90, 81
Bykov, K. M., Kurtsin, I. T. *Kortiko-vistseralnaya patologiya* (Corticovisceral Pathology). Leningrad, 1960
Cairns, A., Constantinides, P. *Science*, 1954, 120, 31
Cannon, W. B. *The Wisdom of the Body*. New York, 1939
Chambers, W. N., *New Engl. J. Med.*, 1946, 235, 347
Chapman, J. M., Massey, F. J. *J. Chron. Dis.*, 1964, 17, 933
Chapman, M. G., Pearce, M. L. *Circulation*, 1957, 16, 558
Chazov, E. I. Rol narusheniya protivosvertyvayushchikh mekhanizmov v vozniknovenii koronarnogo tromboza i novy metod ego lecheniya (The Role of Disturbances in the Anticoagulative Mechanisms in the Appearance of Coronary Thrombosis and the New Method of Its Treatment). Diss. Moscow, 1963
Chazov, E. I. *Kardiologiya* (Cardiology), 1965, 4, 3
Chazov, E. I. *Trombozy i embolii v klinike vnutrennikh boleznei* (Thromboses and Embolisms in the Clinic of Internal Diseases). Moscow, 1966
Chazov, E. I. In: *Serdechnaya i koronarnaya nedostatochnost* (Heart and Coronary Failure). Moscow, 1966, 199

Chazov, E. I. In: *Aktualnye problemy serdechno-sosudistoi patologii* (Urgent Problems of Cardiovascular Pathology). Moscow, 1967, 62
Chazov, E. I. *Kardiol.*, 1970, 7, 5
Chazov, E. I., Andreenko, G. V. *Kardiol.*, 1962, 4, 59
Chazov, E. I., Ruda, M. Y. In: *Aktualnye voprosy kardiologii* (Urgent Problems of Cardiology). Leningrad, 1967, 179, 43
Chazov, E. I., Smetnev, A. S. In: *Shok pri infarkte miokarda* (Shock in Myocardial Infarction). Moscow, 1969, 23
Chazov, E. I., Pershakova, L. P., Ilyushina, I. P. *Ter. arkh.*, 1965, 3, 48
Chazov, E. I., Pushkar, Y. T., Bakumenko, M. S. *et al. Ter. arkh.*, 1964, 7, 13
Chazov, E. I., Smetnev, A. S., Petrova, L. I. *et al. Kardiol.*, 1969, 7, 17
Chazov, E. I., Zysko, A. P., Ruda, M. Y. *Ter. arkh.*, 1966, 11, 52
Cherenko, M. P. *Vrach. delo*, 1960, 3, 265
Chernigovsky, V. N. *Bull. eksper. biol. i med.*, 1943, 15, 1-2, 31
Chernov, A. Z., Kechker, M. I. In: *Prakticheskoe rukovodstvo po klinicheskoi elektrokardiografii* (Practical Guide in Clinical Electrocardiography). Moscow, 1966, 5
Chernov, A. Z., Fradkina, V. Y., Bogoradskaya, M. G. *Ter. arkh.*, 1964, 6, 3
Chernogorov, I. A. *Narusheniya ritma serdtsa* (Disturbances in Cardiac Rhythm). Moscow, 1962
Chernogorov, I. A., Kozhevnikov, Y. A. In: *Nedostatochnost serdtsa i aritmii* (Heart Failure and Arrhythmias). Leningrad, 1966, 311
Chernogorsky, I., Dushek, I. *Cor et vasa*, 1963, 5, 161
Chernyshova, Y. V. In: *Ateroskleroz* (Atherosclerosis). Moscow, 1953, 118
Chrisakis, G. J., Rinzler, S. H., Archer, M. *et al. Amer. J. Clin. Nutr.*, 1965, 16, 243
Civiero, G., Facchini, G., Garbini, G. C. *et al. Arch. Path. Clin. Med.*, 1959, 36, 340
Clagett, A. H. *Circulation*, 1958, 18, 548
Clauss, R. H. *et al. J. Thorac. Cardiovasc. Surg.*, 1961, 41, 447
Clawson, B. J. *Amer. Heart J.*, 1941, 22, 607
Cliffton, E. E. *Amer. J. Cardiol.*, 1960, 6, 476
Cohnheim, J., von Schultess-Rechberg, A. *Arch. Path. Anat.*, 1881, 85, 503
Collis, J. I., Mackinnon, J., Raison, J. C. *et al. Lancet*, 1962, 2, 172
Constantinides, P. *J. Atheroscler. Res.*, 1966, 6, 1
Cook, R. W., Edwards, J. E., Pruitt, R. D. *Circulation*, 1958, 18, 603
Cook, R. W., Edwards, J. E., Pruitt, R. D. *Circulation*, 1958, 18, 613
Cooley, D. A., Belmonte, B. A., Zeiss, L. B. *et al. Surgery*, 1957, 41, 930
Coon, W. W., Duff, I. F. *J. Lab. Clin. Med.*, 1958, 51, 381
Copeman, W. *Textbook of the Rheumatic Diseases.* London, 1969
Cordey, E., Bergman, H. C., Schwartz, L. L. *et al. Amer. Heart J.*, 1949, 37, 560
Cordey, E., Rothenberg, S. F., Rutnam, T. J. *Arch. Neurol. Psychiat.*, 1953, 69, 551
Cox, J. L., McLaughlin, V. W., Flowers, N. C. *et al. Amer. Heart, J.*, 1968, 76, 650
Crainicianu, A. L. *Arch. Path. Anat.*, 1913, 213, 3
Crainicianu, A. L. *Arch. Path. Anat.*, 1922, 238, 1
Crawford, M. D., Morris, J. N. *Brit. Med. J.*, 1960, 2, 1624
Creen, H. D., Kepchar, J. H. *Physiol., Rev.*, 1959, 39, 617
Cronin, R. F. *Curr. Med. Pract.*, 1967, 11, 157
Cronin, R. F. *Amer. Heart J.*, 1966, 72, 282
Cronin, R. F., Moore, S., Marpole, D. G. *Canad. Med. Ass. J.*, 1965, 93, 57
Cutts, F. B., Merlino, F., Easton, F. *Circulation*, 1957, 16, 599
Damir, A. M., Sidorovich, S. Kh., *Ter. arkh.*, 1961, 33, 7, 3
Damir, A. M., Sidorovich, S. Kh., Maminova, V. I. *Klin. med.*, 1960, 2, 33
Danilov, A. A. *Referaty rabot uchrezhdenii otdeleniya biologicheskikh nauk AN SSSR za 1940 g.* (Abstracts of Studies Carried out by Institutions of the Department of Biology, USSR Academy of Sciences in 1940). Moscow-Leningrad, 1941, 322

Danilova, K. M. *Arkh. pat.*, 1961, 11, 11
Danilyak, I. G. *Ter. arkh.*, 1962, 6, 46
Danilyak, I. G. *Vrach. delo*, 1965, 4, 145
Danis, Y. *Tezisy dokladov nauchnoi konferentsii kardiologov Litovskoi SSR* (Theses of Reports to the Scientific Conference of Cardiologists of the Lithuanian SSR). Kaunas, 1964, 32
Daraseliya, I. N. In: *Epidemiologiya arterialnoi gipertonii i koronarnogo ateroskleroza* (Epidemiology of Arterial Hypertension and Coronary Atherosclerosis). Moscow, 1969, 2, 101
Daraseliya, I. N., Milorava, T. D. *Materialy dokladov 7-go soveshchaniya po epidemiologii ishemicheskoi bolezni serdtsa, ateroskleroza i gipertonicheskoi bolezni* (Proceedings of the Seventh Conference on Epidemiology of the Ischaemic Heart Disease, Atherosclerosis and Hypertensive Vascular Disease). Moscow, 1969, 25
Darrow, D. C., Miller, H. C. *J. Clin. Invest.*, 1942, 21, 601
Datey, K. K., Hansoti, R. C., Pandya, V. N. *J.A.M.A.*, 1962, 182, 1078
Davenport, A. B. *Amer. J. Med. Sci.*, 1928, 176, 62
Davgyallo, G. Kh. *Zdravookhr. Belorussii*, 1957, 9, 70
Davydovsky, I. V. *Voprosy lokalizatsii i organopatologii v svete ucheniya Sechenova-Pavlova-Vvedenskogo* (Problems of Localization and Organopathology in the Light of the Sechenov-Pavlov-Vvedensky Teaching). Moscow, 1954
Davydovsky, I. V. *Patologicheskaya anatomiya i patogenez boleznei cheloveka* (Pathological Anatomy and Pathogenesis of Human Diseases). Moscow, 1958, 2, 57
Davydovsky, I. V. Chastnaya patologicheskaya anatomiya (Special Pathological Anatomy). Moscow, 1965
Dawber, T. R., Kannel, W. B., Revotskie, N. *et al. Amer. J. Publ. Health*, 1959, 49, 1349
Day, H. W. *Amer. J. Cardiol.*, 1965, 15, 51
Day, H. W. *Amer. J. Cardiol.*, 1968, 21, 252
Dayton, S., Pearce, M. L., Hashimoto, S. *et al. Circulation*, 1969, 40, Suppl. 2, p. 11-12
Dekhtyar, G. Y. *Elektrokardiograficheskaya diagnostika* (Electrocardiographic Diagnosis). Moscow, 1966
Deming, Q. B. *Bull. N.Y. Acad. Med.*, 1968, 44, 968
Denney, J. L. *et al. J.A.M.A.*, 1956, 161, 614
Desmarest, E. *Presse méd.*, 1934, 42, 811
Desyatov, V. P. *Trudy 2-i Pavlovskoi konferentsii Tomskogo meditsinskogo instituta* (Transactions of the Second Pavlov Conference of the Tomsk Medical Institute). Tomsk, 1952, 51
Deutsch, E. *Münch. Med. Wschr.*, 1962, 104, 1490
Deutsch, E., Fischer, M. *Thrombos. Diathes. Haemorrh.*, 1960, 4, 482
Dewar, H. A., Stephenson, P., Horler, A. R. *et al. Brit. Med. J.*, 1963, 5335, 915
Diaz-Rivera, R. S., Miller, A. J. *Amer. Heart J.*, 1948, 35, 126
Dibner, R. D. *Sov. med.*, 1960, 3, 60
Di Cantogno, L., Chiche, P., Baillet, J. *Arch. Inst. Cardiol. Mex.*, 1959, 29, 65
Dietzman, R. H., Lillehei, C. W. *Amer. Heart J.*, 1968, 75, 136
Dikareva, Y. A. *Arkh. pat.*, 1959, 7, 43
Dikareva, Y. A. *Trudy Voronezhskogo meditsinskogo instituta* (Transactions of the Voronezh Medical Institute). Voronezh, 1961, 43, 92
Dikareva, Y. A. K voprosam kliniki i morfologii anevrizmy serdtsa (Concerning the Clinical Aspects and Morphology of Cardiac Aneurysm). Diss. Voronezh, 1964
Dikshtein, E. A. *Trudy 4-i Vsesoyuznoi konferentsii patologoanatomov* (Transactions of the Fourth All-Union Conference of Pathoanatomists). Moscow, 1956, 280
Djordjevic, B.-S., Bozinovic, L. *Actual. cardiol.*, 1966, 15, 109
Dobrovolskaya, T. I. *Materialy nauchnoi konferentsii 2-go Moskovskogo meditsinskogo instituta im. N. I. Pirogova po probleme 'Ateroskleroz i koronarnaya*

nedostatochnost' (Proceedings of the Scientific Conference of the N. I. Pirogov Second Moscow Medical Institute on the Problem of 'Atherosclerosis and Coronary Failure'). Moscow, 1963, 39
Dobrovolskaya, T. I. *Klin. med.*, 1965, 3, 63
Dock, W. *Med. Clin. N. Amer.*, 1962, 46, 1599
Dodashvili, M. I. *Klinika i diagnostika anevrizmy serdtsa* (Clinical Aspects and Diagnosis of Cardiac Aneurysm). Diss. Moscow, 1956
Dolgoplosk, N. A. *Klin. med.*, 1955, 1, 29
Dolgoplosk, N. A., Shadur, M. G. *Ter. arkh.*, 1955, 4, 79
Donaldson, V. H. *J. Lab. Clin. Med.*, 1960, 56, 644
Donomae, J., Matsumoto, I., Kokubu, I. *et al. Jap. Heart J.*, 1962, 3, 423
Dorofeeva, Z. Z. Eksperimentalnoe issledovanie krovosnabzheniya v uchastkakh ostroi ishemii miokarda s vvedeniem radioizotopa fosfora P^{132} (Experimental Study of the Blood Supply in Parts of Acute Myocardial Ischaemia with Administration of Radioactive Phosphorus P^{132}). Diss. Moscow, 1952
Doshchitsyn, V. L. *Kardiol.*, 1968, 2, 109
Doshchitsyn, V. L., Arshakuni, R. O., Zharov, E. I. *Kardiol.*, 1967, 8, 32
Douglas, A. H., Marienberg, L. *N.Y. St. Med.*, 1949, 49, 2845
Doyle, J. T. In: W. Raab. *Prevention of Ischemic Heart Disease.* Springfield, 1966, 186
Doyle, J. T., Dawber, T. R., Kannel, W. B. *et al. New Engl. J. Med.*, 1962, 26, 796
Doyle J. T., Dawber, T. R., Kannel, W. B. *et al. J.A.M.A.*, 1964, 190, 886
Doyle, J. T., Heslin, A. S., Hilleboe, H. E. *et al. New Engl. J. Med.*, 1959, 261, 1096
Dressler, W. *Amer. Heart J.*, 1959, 57, 501
Dressler, W. *Arch. Intern. Med.*, 1959, 103, 28
Dubrovskya, M. K. Postinfarktny pleche-reberny sindrom (Postinfarction Costobrachial Syndrome). Diss. Moscow, 1968
Eckenhoff, J. E., Hafkenschiel, J. H. *J. Pharmacol. Exp. Ther.*, 1947, 91, 362
Eckenhoff, J. E., Hafkenschiel, J. H., Landmesser, C. M. *et al. Amer. J. Physiol.*, 1947, 149, 634
Eckerström, S. *Acta Med. Scand.*, 1951, suppl. 250, p. 5
Eckstein, R. W., Newberry, W. B., McEachen, J. A. *et al. Circulation*, 1951, 4, 534
Eckstein, R. W., Roberts, J. I., Gregg, D. E. *et al. Amer. J. Physiol.*, 1941, 132, 648
Eckstein, R. W., Stroud, M., Dowling, C. V. *et al. Amer. J. Physiol.*, 1950, 163, 539
Edmondson, H. A., Hoxie, H. J. *Amer. Heart J.*, 1942, 24, 719
Effert, S., Grosse-Brockhoff, F. *Dtsch. med. Wschr.*, 1963, 88, 2165
Ehrlich, J. C., Shinohara, Y. *Circulation*, 1962, 26, 710
Eichna, L. W. *Amer. Heart J.*, 1967, 74, 848
Elek, S. R., Allenstein, B. J., Kornbluth, A. W. *et al. Amer. Heart J.*, 1954, 47, 477
Elgort, P. Y. Izmenenie sistemy krovi pri experimentalnom narushenii koronarnogo krovoobrashcheniya (Change in the Blood System in an Experimental Disturbance in Coronary Circulation). Diss. Moscow, 1966
Elkonkin, B. L., Shimelinovich, L. B. *Trudy Tsentralnogo Instituta Usovershenstvovaniya Vrachei* (Transactions of the Central Institute of Postgraduate Medical Training). Moscow, 1964, 66, 200
Ermilov, L. P. *Kardiol.*, 1962, 1, 37
Ershova, N. V. *Ter. arkh.*, 1966, 12, 34
Ellman, Ph. *Proc. Roy. Soc. Med.*, 1904, 27, 1468
Epstein, F. H. *J. Chron. Dis.*, 1965, 18, 735
Epstein, F. H. *J.A.M.A.*, 1967, 201, 795
Epstein, F. H., Francis, T., Hayner, N. S. *et al. Amer. J. Epidem.*, 1965, 81, 307

Etinger, Y. G. *Mediko-biol. zh.*, 1929, 2, 3
Evans, C.W.F., Graybiel, C.A.G. *Amer. Heart J.*, 1948, 35, 485
Evdokimov, V. F., Yutanov, V. I., Plakhtin, D. L. *Kratkoe soderzhanie dokladov itogovoi nauchnoi konferentsii Lvovskogo meditsinskogo instituta* (Brief Content of the Reports to the Concluding Scientific Conference of the Lvov Medical Institute). Lvov, 1966, 182
Ezerietis, E. T. *Eksper. khir.*, 1959, 5, 16
Fatenkov, V. N. K voprosu o vozmozhnosti autosensibilizatsii pri infarkte miokarda (klinicheskie i eksperimentalnye nablyudeniya) (Concerning the Possibility of Autosensitization in Myocardial Infarction of Clinical and Experimental Findings). Diss. Moscow, 1963
Fatenkov, V. N. K voprosu o vozmozhnosti autosensibilizatsii pri infarkte miokarda (Concerning the Possibility of Autosensitization in Myocardial Infarction). Diss. Kazan, 1964
Fatenkov, V. N. O nekotorykh aspektakh patogeneza, kliniki i lecheniya ostrogo infarkta miokarda (Some Aspects of the Pathogenesis, Clinical Picture and Treatment of Acute Myocardial Infarction). Diss. Kuibyshev, 1969
Fernandez, P. R., Alvarado, M. M. *Arch. Inst. Cardiol. Mex.*, 1967, 37, 208
Fernex, M. *Helv. med. Acta*, 1961, 28, 534
Fernex, M., Sternby, N. H. *Acta Path. Microbiol. Scand.*, 1964, 62, 525
Filipchenko, Y. M., Zhilov, M. S., Gulo, L. F. *et al. Organizatsiya i rabota 'Tsentra po Borbe s tromboembolicheskimi zabolevaniyami'* (The Organization and Work of the 'Centre for Controlling Thromboembolic Diseases'). Leningrad, 1961
First, S. R., Bayley, R. H., Bedford, D. R. *Circulation*, 1950, 2, 31
Fishberg, A. M., Hitzig, W. M., King, F. H. *Arch. Intern. Med.*, 1934, 54, 997
Fleming, J., Hamer, J. *Brit. Heart J.*, 1967, 29, 257
Fletcher, A. P., Sherry, S. *Circulation*, 1960, 22, 619
Fletcher, G. F., Hurst, J. W., Schlant, R. C. *Amer. Heart J.*, 1968, 75, 319
Fodor, J. *et al. Cor et vasa*, 1958, 10, 38
Fogelson, L. I. *Klin. med.*, 1938, 10, 1284
Fogelson, L. I. *Bolezni serdtsa i sosudov* (Diseases of the Heart and Vessels). Moscow, 1951
Fogelson, L. I. *Klinicheskaya elektrokardiologiya* (Clinical Electrocardiology). Moscow, 1957
Fokht, A. B. *O funktsionalnykh i anatomicheskikh narusheniyakh serdtsa pri zakrytii venechnykh arterii* (Concerning the Functional and Anatomic Heart Disturbances on Occlusion of the Coronary Arteries). Moscow, 1901
Ford, R. V., Levine, H. D. *Ann. Intern. Med.*, 1951, 34, 998
Forster, G., Holzmann, M. *Schweiz. med. Wschr.*, 1967, 97, 216
Fowler, N. O., Holwes, J. C. *Circulat. Res.*, 1964, 14, 191
Fox, S. M., Skinner, J. S. *Amer. J. Cardiol.*, 1964, 14, 731
Frankina, B. Y. *Ter. arkh.*, 1956, 6, 32
Franc, C. W. *Bull N.Y. Acad. Med.*, 1968, 44, 900
Frank, E. D. *et al. Amer. J. Physiol.*, 1956, 186, 74
Friedberg, C. K. *Diseases of the Heart.* Philadelphia, 1966
Friedberg, C. K., Horn, H. *J.A.M.A.*, 1939, 112, 1675
Friedman, S., White, P. D. *Ann. Intern. Med.*, 1944, 21, 778
Fröhlich, E. D., Dustan, H. P., Page, I. H. *Arch. Intern. Med.*, 1966, 117, 614
Frowent, R., Lenegre, J., Gonin, A. *et al. Sem. Hôp.*, 1961, 37, 3343
Frumin, M. J., Salanitre, E., Rackow, H. *J. Appl. Physiol.*, 1961, 16, 720
Gabor, A. A. In: *Congr. Cardiol. Internat.* Bratislava, 1967, 53
Galakhov, I. Y. *Kardiol.*, 1970, 4, 64
Ganelina, I. Y. *Kardiol.*, 1970, 7, 152
Ganelina, I. Y., Brikker, V. N., Volpert, Y. I. *Ostryi period infarkta miokarda* (The Acute Period of Myocardial Infarction). Leningrad, 1970
Ganulich, T. V. K morfologii khronicheskoi anevrizmy serdtsa (Concerning the Morphology of Chronic Cardiac Aneurysm). Diss. Kharkov, 1967

Garb, S. *Proc. Soc. Exp. Biol.*, 1950, 73, 134
Gefter, A. I. *Klin. med.*, 1951, 12, 37
Gefter, A. I. In: *Lechenie antikoagulyantami fibrinoliticheskimi sredstvami* (Treatment with Anticoagulants and Fibrinolytic Agents). Kaunas, 1967, 26
Gefter, A. I., Matusova, A. P. *Sov. med.*, 1955, 8, 22
Gefter, A. I., Matusova, A. P. *Ter. arkh.*, 1962, 8, 41
Gefter, A. I., Ponomareva, A. G. *Materialy konferentsii po probleme svertyvaniya krovi* (Proceedings of the Conference on the Problem of Blood Coagulation). Baku, 1966, 74
Gefter, V. A. *Ter. arkh.*, 1960, 10, 76
Gefter, V. A. *Ter. arkh.*, 1963, 2, 22
Gelshtein, E. M. *Infarkt miokarda* (Myocardial Infarction). Moscow, 1948
Geld, H. van der. *Lancet*, 1964, 2, 617
Gelshtein, E. M. *Infarkt miokarda* (Myocardial Infarction). Moscow, 1948; 1951
Gerke, A. A. *Zabolevaniya okoloserdechnoi sumki i ikh lechenie* (Diseases of the Pericardium and Their Treatment). Moscow, 1950
Gerke, A. A. *Kardiol.*, 1969, 10, 30
Gerola, A., Feinberg, H., Katz, L. N. *Amer. J. Physiol.*, 1959, 196, 394
Gershberg, A. L. *Kardiol.*, 1967, 9, 147
Gertler, M. M., White, P. D. *Coronary Heart Disease in Young Adults. A Multidisciplinary Study.* Cambridge, 1954
Gertler, M. M., White, P. D., Cady, L. D. *et al. Amer. J. Med. Sci.*, 1964, 248, 377
Gertler, M. M., Woodbury, M. A., Gottsch, L. G. *et al. J.A.M.A.*, 1959, 170, 149
Gertsen, V. E. Diagnostika anevrizmy serdtsa (Kliniko-elektrofiziologicheskoe issledovanie) (Diagnosis of Cardiac Aneurysm. Clinico-electrophysiological Study). Diss. Sverdlovsk, 1966
Giese, W., Müller-Mohnssen, H. B. In: *Probleme der Coronardurchblutung*. Berlin, 1958, 159
Gilbert, N. C. *J.A.M.A.*, 1939, 113, 1925
Gilbert, N. C., Nalefski, L. A. *J. Lab. Clin. Med.*, 1949, 34, 797
Glagolev, S. I. *Klin. med.*, 1937, 10/11, 1316
Glazova, O. I. In: *Voprosy ostroi vnutrennei kliniki* (Problems of Acute Internal Clinic). Moscow, 1949, 45
Glazova, O. I. *Ibid.*, p. 259
Glazova, O. I. *Klin. med.*, 1956, 9, 17
Glazunov, I. S. *Kardiol.*, 1961, 3, 30
Glukhenky, T. T. *Klin. med.*, 1965, 6, 116
Glukhova, P. A. *Ter. arkh.*, 1966, 9, 27
Glukhova, P. A., Sokolova, R. I. *Kardiol.*, 1968, 7, 41
Goder, G. Z. *Kreisl.-Forsch.*, 1960, 49, 105
Gofman, J. W., Young, W. In: *Atherosclerosis and Its Origin.* New York, 1963
Goldberg, G. A. In: *Rasprostranenie gipertonicheskoi bolezni i koronarnogo ateroskleroza i usloviya zhizni* (Distribution of the Hypertensive Vascular Disease and Coronary Atherosclerosis, and the Conditions of Life). Leningrad, 1964, 53
Goldberg, N. A. *Kardiol.*, 1968, 10, 12
Goldberg, N. A. In: *Ateroskleroz i koronarnaya nedostatochnost. Materialy 20-i godichnoi nauchnoi sessii Instituta kardiologii AMN SSSR* (Atherosclerosis and Coronary Failure. Proceedings of the 20th Annual Scientific Session of the Institute of Cardiology, USSR Academy of Medical Sciences). Moscow, 1969, 47
Goldstein, F., Israel, H. L., Seligson, D. *New Engl. J. Med.*, 1956, 254, 746
Gollwitzer-Meier, K., Kramer, K., Krüger, E. *Arch. ges. Physiol.*, 1936, 237, 639
Golovash, K. M. Primenenie antikoagulyanta dikumarina pri infarkte miokarda. (Use of Dicoumarin [Anticoagulant] in Myocardial Infarction). Diss. Dniepropetrovsk, 1956

Goltsman, A. V., Dmitrieva, I. T. *Osnovy elektrokardiografii* (Fundamentals of Electrocardiography). Kiev, 1960
Goodal, F., Thomas, W. A., O'Neal, R. M. *Arch. Pathol.*, 1960, 69, 599
Gordienko, V. M., Gnesina, E. D., Ruzhitskaya, L. V. *Vrach. delo*, 1964, 2, 137
Gorlin, R., Brachfeld, N., McLeod, C. *et al. Circulation*, 1959, 19, 705
Gornak, K. A. *Arkh. pat.*, 1960, 11, 34
Gornak, K. A. Morfologiya i morfogenez anevrizmy serdtsa i reparativnykh protsessov pri ee khirurgicheskom lechenii (Morphology and Morphogenesis of Cardiac Aneurysm and Reparative Processes in Its Surgical Treatment). Diss. Moscow, 1967
Gornak, K. A., Lushnikov, E. F. *Arkh. pat.*, 1963, 1, 14
Gorokhovsky, B. I. *Ter. arkh.*, 1964, 12, 19
Gotsman, M. S., Schrire, V. S. *Afr. Med. J.*, 1967, 41, 1166
Gould, S. E., Cawley, L. P. *Arch. Intern. Med.*, 1958, 101, 524
Gracheva, G. V., Ivanova, N. V. *Kardiol.*, 1969, 4, 89
Grant, R. P. *Clinical Electrocardiography. The Spatial Vector Approach.* New York, 1957
Grant, R. P. In: *Progr. Cardiovasc. Dis.*, 1959, 2, 237
Gregg, D. E. *Coronary Circulation in Health and Disease.* Philadelphia, 1950
Griffith, G. C., Leak, D., Hegde, B. *Ann. Intern. Med.*, 1962, 57, 254
Grinberg, Ya. M. *Kardiol.*, 1963, 1, 83
Grinberg, Ya. M., Fokina, A. V., Smirnov, I. M. *Trudy Kuibyshevskogo meditsinskogo instituta* (Proceedings of the Kuibyshev Medical Institute). Kuibyshev, 1962, 22, 90
Grishman, A., Scherlis, L. *Spatial Vectorcardiography.* Philadelphia, 1952
Groom, D. *Ann. Intern. Med.*, 1961, 55, 51
Gross, H., Sternberg, W. H. *Arch. Intern. Med.*, 1939, 64, 249
Gross, L. *The Blood Supply to the Heart in Its Anatomical and Clinical Aspects.* New York, 1921
Gross, U. R. In: *Nekotorye problemy sovremennoi vnutrennei meditsiny* (Certain Problems of Modern Internal Medicine). Tallinn, 1964, 63
Grotel, D. M. *Ostryi infarkt miokarda* (Acute Myocardial Infarction). Leningrad, 1940
Gukasian, A. G., Tapitser, E. I. *Ter. arkh.*, 1962, 4-13
Gulo, L. F. Klinika, gematologicheskie izmeneniya, narusheniya ritma i provodimosti v ostreishem periode infarkta miokarda (Clinical Aspects, Hematological Changes, Disturbances in Rhythm and Conduction during the Acutest Period of Myocardial Infarction). Diss. Leningrad, 1965
Gurevich, M. A. *Ter. arkh.*, 1960, 10, 46
Gurevich, M. A., Kelman, I. M. *Kardiol.*, 1968, 10, 18
Gurova, A. M. Tireotoksikoz i tireokardialnye sindromy v klinike vnutrennikh boleznei (Thyrotoxicosis and Thyrocardiac Syndromes in the Clinic of Internal Diseases). Diss. Sverdlovsk, 1964
Gurvich, N. L. *Fibrillyatsia i defibrillyatsia serdtsa* (Fibrillation and Defibrillation of the Heart). Moscow, 1957
Gurvich, N. L. In: *Osnovy reanimatologii* (Fundamentals of Reanimatology). Moscow, 1966, 62
Gusman, S. M. *Materialy 20-i vyezdnoi nauchnoi sessii Azerbaidzhanskogo instituta usovershenstvovaniya vrachei v g. Stepanakerte* (Proceedings of the 20th Itinerant Scientific Session of the Azerbaijan Institute of Postgraduate Medical Training in the City of Stepanakert). Baku, 1961, 13, 27
Gusman, S. M. *Ibid.*, p. 27
Gusman, S. M. *Ter. arkh.*, 1962, 10, 32
Gusman, S. M. *Tezisy dokladov nauchno-prakticheskoi konferentsii klinicheskoi bolnitsy No. 3* (Theses of Reports to the Scientific and Practical Conference of Hospital No. 3). Baku, 1962, 29
Gvatua, N. A. *Ter. arkh.*, 1957, 8, 17
Haas, H. *Arzneimittel-Forsch.*, 1958, 8, 20

Haimovici, H. *Angiology*, 1950, 1, 20
Halpern, M., Weinberg, S. *Circulation*, 1957, 16, 482
Halpert, B., Erikson, E., Gyorkey, F. *Arch. Path.*, 1956, 62, 391
Hammer, A. *Wien. med. Wschr.*, 28, 97-102
Hanbury, W. J. *Brit. Heart J.*, 1957, 19, 435
Hansen, P. F., Geill, T., Lund, E. *Lancet*, 1962, 2, 1193
Harkavy, J., Perlman, E. *Ann. N.Y. Acad. Sci.*, 1960, 90, 327
Harlan, W. R., Osborne, R. K., Graybiel, A. *Circulation*, 1962, 26, 530
Heinonen, I. M. *Sbornik rabot Sverdlovskogo meditsinskogo instituta* (Collection of Papers of the Sverdlovsk Medical Institute). Sverdlovsk, 1965, 45, 129
Heinonen, I. M. In: *Nedostatochnost serdtsa i aritmii* (Heart Failure and Arrhythmias). Leningrad, 1966, 242
Helander, S. *Cardiologia*, 1949/50, 15, 347
Heller, M. L., Watson, T. R. *Anesthesiology*, 1962, 23, 219
Hellerstein, H. K., Martin J. W. *Amer. Heart J.*, 1947, 33, 443
Hellerstein, H. K., Turrel, D. J. *Circulation*, 1958, 18, 735
Heptinstall, R. H., Barkley, H., Porter, K. A. *Angiology*, 1958, 9, 84
Hess, H. *Therapiewoche*, 1967, 17, 1617
Heyden, S. *Proceedings of the Internat. Congress of Nutrition*. Hamburg, 1966, 72
Heyden, S., Heyman, A. *Circulation*, 1967, 35, 141
Higgins, I. T., Cochrane, A. L., Thomas, A. J. *Brit. J. Prev. Soc. Med.*, 1963, **17, 153**
Higgins, I. T., Kannel, W. B., Dawber, T. R. *Brit. J. Prev. Soc. Med.*, 1965, 19, 53
Hochrein, M. *Der Myokardinfarkt*, 1945, 3 Aufl., 384
Hochrein, M., Schleicher, I. *Ther. Umsch.*, 1963, 20, 128
Hoffman, B. F. *Bull. N.Y. Acad. Med.*, 1959, 35, 689
Holmberg, S., Bergman, H. *Acta Med. Scand.*, 1967, 181, 297
Holzmann, M. *Amer. Heart. J.*, 1955, 50, 407
Hoppenstein, R., Clarke, R. L., Cliffton, E. E. *J. Surg. Res.*, 1962, 2, 382
Horn, H., Field, L. E., Dack, S. *et al. Amer. Heart J.*, 1950, 40, 63
Horn, R. C., Fine, G. In: *The Aetiology of Myocardial Infarction*. London, 1963, 229
Hudson, R. *Cardiovascular Pathology*. London, 1965, v. 1, p. 660
Hunter, A. L., Insall, J. N. *Brit. Med. J.*, 1959, 5132, 1282
Hunter, F. E., Kanana, S., Ford, Z. *Fed. Proc.*, 1953, 12, 221
Hurwitz, M., Eliot, R. S. *Dis. Chest.*, 1964, 45, 616
Iliychenko, V. Y. Nekotorye pokazateli sostoyaniya gipofizarno-nadpochechnikovoi sistemy u bolnykh infarktom miokarda (Some Indices of the State of the Hypophyseal-Adrenal System in Myocardial Infarction Patients). Diss. Kiev, 1965
Ilyinsky, S. P. Materialy k patologicheskoi anatomii sosudov Viessana-Tebeziya (Materials for the Pathological Anatomy of the Veins of Vieussens-Thebesius). Diss. Moscow, 1952
Ilyushina, I. P., Kudryashov, B. A. *Kardiol.*, 1963, 4, 65
Imhof, P., Brunner, H., Quitt, J. *et al. Schweiz. med. Wschr.*, 1964, 94, 1119
Ioffe, V. I. *Vestn. AMN SSSR*, 1963, 11, 3
Iosava, K. V. Narkoz zakisiyu azota pri bolevom sindrome ostroi koronarnoi nedostatochnosti (Nitrous Oxide Anaesthesia in the Pain Syndrome of Acute Coronary Failure). Diss. Moscow, 1965
Ito, V., Kojima, V., Hasegawa, V. *et al. Jap. Heart J.*, 1966, 7, 524
Ivanitskaya, M. A. *Ter. arkh.*, 1950, 6, 26
Ivanov, G. F. *Vestn. khir. i pogran. obl.*, 1932, 78, 79, 3
Ivanova, T. N. *Tezisy dokladov 24-i nauchnoi sessii Arkhangelskogo meditsinskogo instituta* (Theses of Reports to the 24th Scientific Session of the Arkhangelsk Medical Institute). Arkhangelsk, 1960, 19
Ivanova, T. N. Klinika atipichnykh form infarkta miokarda i predynfarktnykh sostoyanii (Clinical Aspects of Atypical Forms of Myocardial Infarction and Pre-infarction States). Diss. Arkhangelsk, 1961
Jacobs, H. D., Elliott, G. A. *Acta med. Scand.*, Suppl. 306, 1955

James, T. N. *Circulation*, 1961, 24, 761
James, T. N. *Amer. Heart J.*, 1962, 64, 416
Jennings, R. B., Sommers, H. M., Smyth, Y. A. *et al. Arch. Path.*, 1960, 70, 68
Jetter, W. W., White, P. D. *Ann. Intern. Med.*, 1944, 21, 783
Johnson, J. R., Di Palma, J. R. *J. Physiol.*, 1939, 125, 234
Jolliffe, N., Baumgartner, L., Rinzler, S. H. *et al. N. Y. St. J. Med.*, 1963, 63, 69
Jordan, R. A., Dry, T. J., Edwards, J. E. *Proc. Staff. Meet. Mayo Clin.*, 1950, 25, 673
Julian, D. G., Valentine, P. A., Miller, G. G. *Amer. J. Med.*, 1964, 37, 915
Kaevitser, I. M. In: *Voprosy klinicheskoi meditsiny i profpatologii* (Problems of Clinical Medicine and Occupational Pathology). Moscow, 1965, 31
Kahn, H. A. *Amer. J. Publ. Health*, 1963, 53, 1058
Kakhnovsky, I. M. Issledovanie perifericheskogo krovoobrashcheniya u bolnykh infarktom miokarda, oslozhnennom kollapsom (po dannym metodov reovazografii, elektroostsillografii i kapillyaroskopii) (Study of the Peripheral Circulation in Patients Suffering from Myocardial Infarction Aggravated by Collapse. According to the Findings of Rheovasography, Electrooscillography and Capillaroscopy) Diss. Moscow, 1965
Kalinina, N. V., Bogoslovsky, V. A. *Tezisy dokladov 13-i nauchnoi sessii Instituta Terapii AMN SSSR* (Theses of Reports to the 13th Scientific Session of the Institute of Therapy, USSR Academy of Medical Sciences). Moscow, 1962, 19
Kalinina, N. V., Bogoslovsky, V. A. In: *Rasprostranenie gipertonicheskoi bolezni i koronarnogo ateroscleroza i usloviya zhizni* (Distribution of the Hypertensive Vascular Disease and Coronary Atherosclerosis, and the Conditions of Life). Leningrad, 1964, 111
Kalishevskaya, T. M. Regulyatornye vzaimootnosheniya svertyvayushchei i protivosvertyvayushchei sistemy krovi (Regulatory Interrelations between the Coagulative and Anticoagulative Systems of the Blood). Diss. Moscow, 1968
Kalitievskaya, V. F. *Arkh. pat.*, 1957, 5, 29
Kaltenbach, J. P., Jennings, R. B. *Circulat. Res.*, 1960, 8, 207
Kamenetsky, S. I., Pesikov, Ya. S. *Vrach. delo*, 1961, 7, 20
Kandel, E. I. Vliyanie ostrogo razdrazheniya razlichnykh otdelov golovnogo mozga cheloveka na krovyanoe davlenie, serdechnuyu deyatelnost i dykhaniye (Influence of Acute Stimulation of Various Parts of the Human Brain on the Blood Pressure, Cardiac Activity and Respiration). Diss. Moscow, 1950
Kandel, E. I. *Vopr. neirokhir.*, 1951, 4, 23
Kannel, W. B., Dawber, T. R., Skinner, J. J. *et al. Circulation*, 1965, Suppl. II. 32, 121; *Amer. J. Publ. Health.* 1965, 55, 1355
Kannel, W. B., Kagan, A., Dawber, T. R. *et al. Geriatrics*, 1962, 17, 675
Kannel, W. B., Le Bauer, J., Dawber, T. R. *Circulation*, 1963, 28, 747
Kannel, W. B., Le Bauer, J., Dawber, T. R. *et al. Circulation*, 1967, 35, 734
Kareva, T. P., Markov, A. M. *Klin. med.*, 1954, 1, 42
Karpova, G. D. Izmeneniya gemodinamiki u lits perenesshikh infarkt miokarda (Changes in Haemodynamics of Persons Who Have Survived Myocardial Infarction). Diss. Moscow, 1966
Karner, H. T., Dwyer, J. E. *J. Med. Res.*, 1916, 34, 21
Kasalitsa, Ch. L. *Sov. med.*, 1960, 1, 63
Kasanen, A., Kallio, V., Forström, J. *Ann. Med. Intern. Fenn.*, 52, Suppl. 43, 1963
Kasatkina, L. V. Rol osnovnogo veshchestva arterii v patogeneze ateroskleroza (Role of the Basic Substance of Arteries in the Pathogenesis of Atherosclerosis). Diss. Moscow, 1969
Kashayev, P. O. Gistogenez rubtsa serdechnoi myshtsy pri pronikayushchikh i nepronikayushchikh raneniyakh (Histogenesis of the Scar in the Heart Muscle in Penetrating and Non-penetrating Wounds). Diss. Rostov-on-Don, 1951

Katz, L. N., Williams, F. L., Laurent, D. *et al. Fed. Proc.*, 1956, 15, 106
Katz, R. L. *Anestesiology*, 1965, 26, 289
Kaulla, K. N., von Schultz, R. L. *Amer. J. Clin. Path.*, 1958, 29, 104
Kaverina, N. V. *Farmakol. i toksikol.*, 1958, 1, 39
Kaverina, N. V. *Bull. eksper. biol. i med.*, 1959, 8, 67
Kazakova, N. V. Krovosnabzhenie serdtsa cheloveka i nekotorykh mlekopitayushchikh zhivotnykh (Blood Supply of the Heart of Man and Some Mammals). Diss. Volgograd, 1955
Kazem-Bek, A. P. *Bolnichnaya gazeta Botkina*, 1896, 12, 241; 13, 274
Kazmina, P. V. *Sov. med.*, 1964, 1, 6
Kechker, M. I., Avrukh, R. L. In: *Prakticheskoe rukovodstvo po klinicheskoi elektrokardiografii* (Practical Manual of Clinical Electrocardiography). Moscow, 1966
Kent, S. P., Diseker, M. *Lab. Invest.*, 1955, 4, 398
Kernig, V. M. *Russk. vrach*, 1904, 44, 1461
Kershbaum, A., Bellet, S. *J.A.M.A.*, 1964, 187, 32
Kershbaum, A., Bellet, S., Caplan, R. F. *et al. Amer. J. Cardiol.*, 1962, 10, 204
Kershbaum, A., Khorsandian, R., Caplan, R. F. *et al. Circulation*, 1962, 26, 743
Kershbaum, A., Khorsandian, R., Caplan, R. F. *et al. Circulation*, 1963, 28, 52
Kertesi, K. *Gyogyszereszet*, 1957, 11, 70
Keys, A. *Atherosclerosis and Its Origin.* New York, 1963
Khamitov, S. Kh. Znachenie izmenenii stenki sosuda v razvitii tromboza venechnykh artery pri koronarnoi nedostatochnosti (The Significance of the Changes in the Vascular Wall in the Development of Coronary Thrombosis in Coronary Failure). Diss. Moscow, 1952
Khamitov, S. Kh. *Trudy Vsesoyuznoi konferentsii patalogoanatomov* (Transactions of the All-Union Conference of Pathoanatomists). Moscow, 1956, 268
Khetagurov, A. D. *Ter. arkh.*, 1961, 10, 33
Khilkevich, B. V. *Trudy 1-go Moskovskogo meditsinskogo instituta* (Transactions of the First Moscow Medical Institute). Moscow, 1965, 36, 165
Khvalibov, Y. V., Federmesser, K. M. *Nauchnye trudy Moskovskoi gorodskoi bolnitsy No. 52* (Scientific Transactions of Moscow Hospital No 52). Moscow, 1961, 259
Kiessling, J. *Münch. med. Wschr.*, 1965, 107, 95
Kikaion, E. E. In: *Ateroskleroz i koronarnaya nedostatochnost* (Atherosclerosis and Coronary Failure). Moscow, 1956, 40.
Kikaion, E. E. In: *Ateroskleroz i infarkt miokarda* (Atherosclerosis and Myocardial Infarction). Moscow, 1959, 5
Kilinsky, Y. L., Kechker, M. I., Zhuk, Y. A. *Ter. arkh.* 1959, 2, 77
Kipshidze, N. N. *Ter. arkh.*, 1957, 7, 40
Kipshidze, N. N., Tripdiani, D. D. In: *Aktualnye problemy serdechnososudistoi patologii* (Urgent Problems of Cardiovascular Pathology). Moscow, 1963, 134
Kirk, J. E. In: *The Aetiology of Myocardial Infarction.* London, 1963, 273
Kisin, I. Y., Sinitsyn, L. N. *Vestn. AMN SSSR*, 1963, 1, 18
Kisin, I. Y., Zubovskaya, A. M. *Farmakol. i toksikol.*, 1964, 4, 446
Klimenko, A. G. *Klin. med.*, 1965, 6, 118
Klinfelder, H. *Dtsch. med. Wschr.*, 1963, 88, 1695
Klionsky, B. *Amer. J. Path.*, 1960, 36, 575
Klocke, F. J., Kaiser, G. A., Ross, J. *et al. Amer. J. Physiol.*, 1965, 209, 913
Klykov, N. V. *Kardiol.*, 1969, 5, 72
Knopf, K. F. Cited in: Kramchaninov, N. F. *et al.*
Kofanov, I. F. In: *Voprosy ostroi vnutrennei kliniki* (Problems of Acute Internal Clinic). Moscow, 1949, 7
Kochetov, A. M. Klinicheskie, instrumentalnye i eksperimentalnye issledovaniya pri anevrizme serdtsa (Clinical, Instrumental and Experimental Studies of Cardiac Aneurysm). Diss. Lvov, 1964
Kogan, B. B. *Trudy 14-go Vsesoyuznogo s yezda terapevtov* (Transactions of the 14th All-Union Congress of Internists). Moscow, 1958, 361
Kogan, B. B., Zharkovskaya, T. S. *Klin. med.*, 1950, 11, 30

Kogan, M. B. *Klin. med.*, 1940, 78, 25
Kokosov, A. N., Heinonen, I. M. *Vengersk. med.*, 1966, 20
Kolesov, A. P. *Vestn. khir.*, 1960, 85, 9, 21
Kolobutina, O. M., *Ter. arkh.*, 1961, 1, 73
Komarova, Y. K. *Ter. arkh.*, 1964, 8, 18
Kondratiev, V. S. *Arkh. pat.*, 1966, 3, 46
König, K., Reindell, H., Hoffmann, G. *Dtsch. med. Wschr.*, 1967, 92, 292
Kononyachenko, V. A., Gerasimova, E. N. *Kardiol.*, 1964, 2, 76
Konstantinov, E. N. In: *Rasprostranenie gipertonicheskoi bolezni i koronarnogo ateroskleroza i usloviya zhizni* (Distribution of Hypertensive Vascular Disease and Coronary Atherosclerosis and the Conditions of Life). Leningrad, 1964, 94
Konstantinov, E. N. In: *Epidemiologiya arterialnoi gipertonii i koronarnogo ateroskleroza* (Epidemiology of Arterial Hypertension and Coronary Atherosclerosis). Moscow, 1969, 2, 64
Konttinen, A. *Brit. Med., J.*, 1962, 5285, 1115
Konyaev, B. V. *Klin. med.*, 1959, 3, 81
Konyaev, B. V., Rudneva, P. A., Viyushina, O. P. *et al. Kardiol.*, 1964, 1, 16
Koreisha, L. A. O roli bolshikh polusharii golovnogo mozga cheloveka v regulyatsii funktsii serdechno-sosudistoi sistemy (Concerning the Role of the Human Big Hemispheres in Regulating the Functions of the Cardiovascular System). Diss. Moscow, 1939
Korovkin, B. F. *Fermenty v diagnostike infarkta miokarda* (Enzymes in the Diagnosis of Myocardial Infarction). Leningrad, 1965
Kowalski, E. *Thrombos. Diathes. Haemorrh.*, 1960, Suppl. 4, 211
Kozhevnikov, U. A. K patogenezu aritmiy pri povrezhdenii miokarda. (Concerning the Pathogenesis of Arrhythmias in Myocardial Injury). Diss. Moscow, 1963
Kozhevnikova, T. L., Andreenko, G. V. In: *Ateroskleroz i tromboz* (Atherosclerosis and Thrombosis). Moscow, 1964, 172
Kozyreva, S. A., Petrova, S. S. *Kardiol.*, 1968, 1, 45
Kramchaninov, N. F., Dyominu, I. N., Popovoi, F. V. and Ginzburg, S. *Klin. med.*, 1966, 1, 153
Krasnow, N., Rolett, E. L., Jurchak, P. M. *et al. Amer. J. Med.*, 1964, 37, 514
Kravkov, N. P. *Osnovy farmakologii* (Fundamentals of Pharmacology). St. Petersburg, 1907
Krister, E E., Sherstnev, K. M., Epshtein, O. I. *et al.* In: *Rasprostranenie gipertonicheskoi bolezni i koronarnogo ateroskleroza i usloviya zhizni* (Distribution of the Hypertensive Vascular Disease and Coronary Atherosclerosis, and the Conditions of Life). Leningrad, 1964, 122
Krol, W., Ciba, T., Kocemba, J. *et al. Pol. Arch. Med. Wewnet.*, 1967, 38, 605
Kruglov, N. A. *Farmakol. i toksikol.*, 1958, 1, 34
Krumbhaar, E. B., Crowell, C. *Amer. J. Med. Sci.*, 1925, 170, 828
Krylov, A. A., Gordienko, Y. A. *Sov. med.*, 1966, 12, 72
Kryukov, A. N. In: *Voprosy ostroi vnutrennei kliniki* (Problems of Acute Internal Clinic). 1949, 35
Kudryashov, B. A. *Problemy svyortyvaniya krovi i tromboobrazovaniya* (Problems of Blood Coagulation and Thrombogenesis). Moscow, 1960
Kudryashov, B. A. *Vopr. med. khimii*, 1960, 6, 1, 3
Kudryashov, B. A., Kalishevskaya, T. M., *Dokl. AN SSSR*, 1960, 131, 1, 213
Kudryashov, B. A., Ulitina, P. D. *Dokl. AN SSSR*, 1958, 120, 3, 677
Kudryashov, B. A., Ushakova, M. B., Bazazian, G. G. *et al. Bull. eksper. biol. i med.*, 1964, 3, 26
Kuhn, L. A. *Amer. Heart J.*, 1967, 74, 578
Kukes, V. G. *Klin. med.*, 1963, 6, 65
Kurland, G. S., Pressman, D. *Circulation*, 1965, 31, 834
Kurshakov, N. A. *Krovoobrashchenie normalnoe i patologicheskoe* (Normal and Pathological Blood Circulation). Moscow, 1947
Kurshakov, N. A., Pressman, L. P. *Krovoobrashchenie v norme i patologii* (Normal and Pathological Blood Circulation). Moscow, 1969

Kushakov, V. I. Funktsii kory nadpochechnikov u bolnykh ostroi koronarnoi nedostatochnostiyu (Functions of the Adrenal Cortex). Diss. Moscow, 1966
Kushelevsky, B. P. *Vrach. delo*, 1955, 12, 1149
Kushelevsky, B. P. *Ocherki po antikoagulyantnoi terapii* (Papers of Anticoagulant Therapy). Moscow, 1958
Kushelevsky, B. P., Gurova, A. M. *Kardiol.*, 1966, 1, 65
Kushelevsky, B. P., Schmidt, Y. D. *Klin. med.*, 1958, 5, 22
Kuzmina-Prigradova, A. V. Predserdno-zheludochkovyi puchok (Gisa) serdtsa cheloveka i ego krovosnabzhenie (The Bundle of His in the Human Heart and Its Blood Supply). Diss. Moscow, 1949
Kyandzuntseva, E. A. In: *Serdechnaya i koronarnaya nedostatochnost* (Heart and Coronary Failure). Moscow, 1966, 150
Kyandzuntseva, E. A., Udelnov, M. G. In: *Voprosy patologii i fiziologii serdtsa* (In book: Problems of Pathology and Physiology of the Heart). Moscow, 1955, 37
Laborit, H. *Presse méd.*, 1963, 71, 1
Laborit, H., Huguenhard, P. *Presse méd.*, 1951, 59, 1329
La Due, J. S., Wroblewski, F., Karmen, A. *Science*, 1954, 120, 497
Lakin, K. M. In: *Lechenie koagulyantami i fibrinoliticheskimi sredstvami* (Treatment with Coagulants and Fibrinolytic Agents). Kaunas, 1967, 106
Lampesis, P. T., Crandall, W. D., King, S. J. *New Engl. J. Med.*, 1953, 248, 455
Lampugnani, P. *Minerva cardiol.*, 1967, 15, 34
Lang, G. F. *Voprosy patologii krovoobrashcheniya* (Problems of Circulatory Pathology). Leningrad, 1936
Lang, G. F. *Bolezni sistemy krovoobrashcheniya* (Diseases of the Circulatory System). Moscow, 1957
Lapin, B. A. *Bull. eksper. biol. i med.*, 1955, 40, 8, 19
Lapin, B. A. *Trudy Vsesoyuznoi konferentsii patologoanatomov* (Transactions of the All-Union Conference of Pathoanatomists). Moscow, 1956, 263
Lashchevker, V. M. *Kardiol.*, 1969, 3, 145
Laskin, S. B. *Klin. med.* 1962, 6, 130
Laszlo, B., Laszlo, K. *Wien. Klin. Wschr.*, 1867, 79, 875
Laurie, W., Woods, J. D. *Lancet*, 1962, 1, 13
Laurie, W., Woods, J. *Acta cardiol.*, 1963, 18, 399
Lavrov, K. A. *Trudy gistologicheskoi konferentsii* (Transactions of the Histological Conference). Moscow, 1949, 3, 223
Lazovsky, U. M. *Funktsionalnaya morfologiya zheludka v norme i patologii* (Functional Morphology of the Stomach in Health and Pathology). Moscow, 1947.
Leary, T. *Amer. Heart J.*, 1935, 10, 338
Lebed, N. S. *Zdravookhr. Byelorussii*, 1961, 2, 51
Lebedeva, V. S. *Vrachebnyi kontrol i lechebnaya fizkultura* (Medical Control and Exercise Therapy). Moscow, 1955, 205
Lebedeva, V. S. *Lechebnaya fizkultura pri infarkte miokarda* (Exercise Therapy in Myocardial Infarction). Leningrad, 1963
Lenerge, J., Gerbaux, A. *Arch. Mal. Coeur.*, 1952, 45, 289
Lepskaya, Y. S. *Kliniko-rentgenologicheskaya diagnostika infarktov legkikh* (Clinico-Roentgenological Diagnosis of Pulmonary Infarctions). Moscow, 1963
Levene, A. *Brit. Heart J.*, 1960, 22, 660
Levi, L. In W. Raab. *Prevention of Ischemic Heart Disease*. Springfield, 1966, 85
Levine, H. D., Ford, R. V. *Circulation*, 1950, 1, 246
Levine, S. A., Brown, C. L. *Coronary Thrombosis. Its Various Clinical Features*. London, 1929
Levine, S. A., Brown, C. *Med. Baltimore*, 1929, 8, 245
Lewis, D. H., Mellander, S. *Acta physiol. Scand.*, 1962, 56, 162
Leyden, E. Z. *Klin. Med.*, 1884, 7, 456
Libanoff, A. J. *Amer. J. Cardiol.*, 1964, 14, 339
Libanoff, A. J., Boiteau, G. M., Allenstein, B. J. *Amer. J. Cardiol.*, 1963, 12, 772

Libman, E. *Trans. Ass. Amer. Phys.*, 1930, 45, 153
Lifshits, A. M., Krylova, A. M., Mebel, N. M. *et al.* In: *Epidemiologiya arterialnoi gipertonii i koronarnogo ateroskleroza* (Epidemiology of Arterial Hypertension and Coronary Atherosclerosis). Moscow, 1969, 2, 109
Likhtenshtein, E. I. *Klin. med.*, 1962, 12, 71
Lillehei, R. C., Longerbeam, J. K., Bloch, J. H. *et al. Ann. Surg.*, 1964, 160, 682
Lisa, J. R., Ring, A. *Arch. Intern. Med.*, 1932, 50, 131
Lisitsyn, M. S. *Vestn. khir. i pogran. obl.*, 1927, 26-27, 222
Litinsky, A. S., Melman, N. Y. *Vrach. delo*, 1962, 5, 137
Litova, I. F. *Kardiol.*, 1967, 8, 102
Lodge-Patch, I. *Brit. Heart J.*, 1951, 13, 37
Loeb, H. S., Pietras, R. J., Gunnar, R. M. *et al. Circulation*, 1968, 37, 210
Logachev, K. D. *Vrach. delo*, 1961, 1, 32
Loginov, A. S. *Sov. med.*, 1961, 7, 19
Lown, B. In: *Acute Myocardial Infarction.* London, 1968, 13
Lown, B., Awarasingham, R., Newman, *J.A.M.A.*, 1962, 182, 548
Lown, B., Fakhro, A. M., Hood, W. B. *et al. J.A.M.A.*, 1967, 199, 188
Lu, F. C., Melville, K. I. *J. Physiol.*, 1951, 113, 365
Luisada, A., Cardi, L. *Circulation*, 1956, 13, 113
Luisada, A. A., Rosa, L. M. In: *Lechenie ostrykh serdechno-sosudistykh narushenii* (Treatment of Acute Cardiovascular Disorders). Moscow, 1964, 18
Lukashevichute, A. In: *Ateroskleroz* (Atherosclerosis). Leningrad, 1965, 128
Lukel, W. T., Lewis, P. H., Enterline, P. E. *et al. Amer. J. Publ. Health*, 1959, 49, 1930
Lukomsky, P. E. *Ter. arkh.*, 1938, 1-2, 39
Lukomsky, P. E. *Ter. arkh.*, 1940, 4, 286
Lukomsky, P. E. *Elektrocardiogramma pri boleznyakh miokarda* (Electrocardiogram in Myocardial Diseases). Moscow, 1943
Lukomsky, P. E. *Kardiol.*, 1962, 3, 3
Lukomsky, P. E. *Kardiol.*, 1963, 4, 8
Lukomsky, P. E. In: *Mnogotomnoe rukovodstvo po vnutrennim boleznyam* (Multivolume Manual of Internal Diseases). Moscow, 1964, 2, 337
Lukomsky, P. E., Doshchitsyn, V. L. *Kardiol.*, 1969, 1, 1
Lukomsky, P. E., Gratsiansky, N. A. *Kardiol.*, 1968, 1, 3
Lukomsky, P. E., Kazmina, P. V. *Kardiol.*, 1961, 4, 3
Lukomsky, P. E., Kazmina, P. V. *Sov. med.*, 1963, 11, 3
Lukomsky, P. E., Kazmina, P. V. In: *Aktualnye problemy serdechnososudistoi patologii* (Urgent Problems of Cardiovascular Pathology). Moscow, 1967, 16
Lukomsky, P. E., Tareev, Y. M. *Sov. med.*, 1957, 1, 3
Lukomsky, P. E., Tareev, Y. M. *Trudy 14-go Vsesoyuznogo s''yezda terapevtov* (Transactions of the 14th All-Union Congress of Internists). Moscow, 1958, 267
Lukomsky, P. E., Lakin, K. M., Kazmina, P. V. *et al. Kardiol.*, 1968, 3, 84
Lukomsky, P. E., Meerson, F. Z., Soloviov, V. V. *et al. Kardiol.*, 1967, 1, 3
Lukomsky, P. E., Soloviov, V. V., Volodin, N. I. *Klin. med.*, 1963, 10, 25
Lukomsky, P. E., Soloviov, V. V., Shenderov, S. M. *et al.* In: *Profilaktika i lechenie koronarnoi i serdechnoi nedostatochnosti* (Prevention and Treatment of Coronary and Heart Failure). Leningrad, 1967, 96
Luria, M. H., Adelson, E. I., Miller, A. J. *Circulation*, 1966, 34, 767
Lushnikov, E. F. Morfologiya okislitelno-vosstanovitelnykh protsessov v serdtse pri eksperimentalnom infarkte miokarda (gistokhimicheskoye issledovaniye) (Morphology of the Oxidation-reduction Processes in the Heart in Experimental Myocardial Infarction. Histochemical Study). Diss, Moscow, 1962
Lysenko, L. T. Issledovanie dezoksiribonukleaz i ikh substrata pri infarkte miokarda (A Study of Desoxyribonucleases and Their Substrate in Myocardial Infarction). Diss. Moscow, 1966
Macrez, C. *Presse med.*, 1967, 75, 2463

Maher, J. F., Mallory, G. K., Laurenz, G. A. *New Engl. J. Med.*, 1956, 255, 1
Makolkin, V. I. *Ter. arkh.*, 1957, 3, 66
Malach, M. *Amer. J. Cardiol.*, 1967, 20, 363
Mallory, G. K., White, P. D., Salcedo-Salgar, J. *Amer. Heart J.*, 1939, 18, 647
Malmcrona, R., Schröder, G., Werkö, L. *Acta med. Scand.*, 1966, 180, 55
Malone, R.G.S., Parkes, W.E., *Brit. Heart J.*, 1955, 17, 448
Malyarovsky, V. N. *Sov. med.*, 1961, 8, 29
Mamilyaev, P. M. Klinikorentgenologicheskie nablyudeniya nad vnutriserdechnymi obyzvestvleniyami (Clinico-radiographic Studies of Intracardiac Calcification). Diss. Moscow, 1964
Mandl, D., Kennedy, I. *Ter. arkh.*, 1958, 5, 56
Manson, D. I., Fullerton, H. W. *Brit. Med. J.*, 1956, 1, 6
Marchetti, G., Maccari, M., Merlo, L. *Cardiologia*, 1963, 42, 1
Marek, Z., Jaegermann, K., Ciba, T. *Amer. Heart J.*, 1962, 63, 768
Marie, R. *L'infarctius du myocarde et ses consequences.* Paris, 1896
Markosian, A. A. *Nervnaya regulyatsiya svertyvaniya krovi* (Nervous Regulation of Blood Coagulation). Moscow, 1960
Martynkin, G. A. *Vrach. delo*, 1962, 9, 39
Martynov, A. V. Khirurgiya podzheludochnoi zhelezy (Surgery of the Pancreas). Diss. Moscow, 1897
Martynov, S. M., Bilynskaya, Z. S. *Klin. med.*, 1967, 6, 81
Mashkovsky, M. D. *Lekarstvennye sredstva* (Medicinal Substances). Moscow, 1967
Mason, J. W., Mangan, G. J., Brady, J. V. *et al. Psychosom. Med.*, 1961, 23, 344
Master, A. M., Dack, S. *Arch. Intern. Med.*, 1949, 64, 767
Master, A. M., Gubner, R., Dack, S. *et al. Arch. Intern. Med.*, 1941, 67, 647
Matusova, A. P. In: *Grudnaya zhaba i infarkt miokarda* (Angina Pectoris and Myocardial Infarction). Gorky, 1960, 321
Matusova, A. P. Problema rezhima pri lechenii bolnykh infarktom miokarda (Problem of the Regimen in the Treatment of Myocardial Infarction Patients). Diss. Gorky, 1964
Matusova, A. P., Morozova, A. P. In: *Voprosy grudnoi i neotlozhnoi khirurgii* (Problems of Thoracic and Urgent Surgery). Gorky, 1958, 115
Matusova, A. P., Kuchina, E. N., Ures, U. A. *et al. Sov. med.*, 1965, 5, 59
Mazur, N. A. *Ter. arkh.*, 1966, 3, 93
Mazur, N. A., Ruda, M., Kats, I. A. *et al. Kardiol.*, 1967, 1, 67
McCain, F. H., Kline, E. M., Gilson, J. S. *Amer. Heart J.*, 1950, 39, 263
McCloy, R. M., Spittell, J. A., McGoon, D. C. *Circulation*, 1965, 31, 665
McDonald, D. E., Terguson, D. *Proc. Soc. Exp. Biol.*, 1966, 121, 626
McDonald, D. E., Bentley, W. B. *New Engl. J. Med.*, 1951, 244, 743
McDonough, J. R., Hames, C. G., Stulb, S. C. *et al. J. Chron. Dis.*, 1965, 18, 443
McGregor, M., Palmer, W. H. In: *Coronary Heart Disease.* New York, 1963, 178
McMahon, B., Pugh, C. F., Ipsen, J. *Epidemiological Methods.* Boston, 1960, 302
McQuay, N. W., Edwards, J. E., Burchell, H. B. *Arch. Intern. Med.*, 1955, 96, 1
Mdinaradze, Y. S. Gemodinamika pri infarkte miokarda (kliniko-eksperimentalnoe issledovanie (Haemodynamics in Myocardial Infarction, Clinico-Experimental Study). Diss. Moscow, 1966
Meciani, L., Tomasini, M. *Minerva cardioangiol.*, 1966, 14, 631
Medzmariashvili, T. G. Vektorkardiograficheskaya diagnostika infarkta miokarda. Kliniko-eksperimentalnye issledovaniya. (Vectorcardiographic Diagnosis of Myocardial Infarction. Clinico-Experimental Studies). Diss. Leningrad, 1967

Meerson F. Z. *Kompensatornaya giperfunktsiya i nedostatochnost serdtsa* (Compensatory Cardiac Hyperfunction and Insufficiency). Moscow, 1960
Meerson, F. Z., Pshennikova, M. G., Pogosian, L. A. *Trudy 1-go Moskovskogo meditsinskogo instituta* (Transactions of the First Moscow Medical Institute). Moscow, 1967, 53, 262
Meerson, F. Z., Pshennikova, M. G., Pogosian, L. A. *et al. Mekhanism kardiotonicheskogo deistviya serdechnykh glikozidov* (Mechanism of Cardiotonic Action of Cardiac Glycosides). Leningrad, 1968
Meerzon, T. I. Cited in: V. S. Nesterov
Meerzon, T. I. Cited in: A. N. Berinskaya *et al.*
Melikova, M. Y. *Klin. med.*, 1956, 4, 23
Melkumova, I. S. *Ter. arkh.*, 1961, 2, 33
Melkumova, I. S. Znachenie opredeleniya nekotorykh biokhimicheskikh pokazatelei krovi dlya rannei diagnostiki infarkta miokarda i stenokardii (Significance of Determining Some Biochemical Indices of the Blood for Early Diagnosis of Myocardial Infarction and Angina Pectoris). Diss. Moscow, 1962
Meltzer, L. E., Kitchell, J. B. In: *Prog. Cardiovasc. Dis.*, 1966, 9, 1, 50
Melville, K. I. *First Intern. Conference of Prevent. Cardiology.* Vermont, 1964, 12
Menshikov, V. V., Usatova, I. Ya. *Materialy nauchnoi konferentsii posvyashch. 15-letiyu Chernovitskogo oblastnogo zobno-endokrinologicheskogo dispansera* (Proceedings of the Scientific Conference on the 15th Anniversary of the Chernovtsy Regional Goiter and Endocrinological Dispensary). Chernovtsy, 1963, 67
Meshalkin, Y. N. In: *Voprosy anesteziologii i operativnoi patofiziologii* (Problems of Anaesthesiology and Surgical Pathophysiology). Moscow, 1959, 5
Meshcheryakova, A. V. Klinicheskoe i farmakodinamicheskoe issledovanie perifericheskogo krovoobrashcheniya pri infarkte miokarda i grudnoi zhabe (Clinical and Pharmacodynamic Study of the Peripheral Circulation in Myocardial Infarction of the Peripheral Circulation in Myocardial Infarction and Angina Pectoris). Diss. Moscow, 1963
Messerich, J. *Med. Welt.* 1966, 36, 1904
Metelitsa, V. I., Kokurina, E. V., Tsarfis, T. P. *et al. Sov. med.*, 1970, 6, 142
Mikhnev, A. L., Zilberman, D. B., Korkushko, O. V. *et al.* In: *Nedostatochnost serdtsa i aritmii (Heart Failure and Arrhythmias).* Leningrad, 1966, 237
Miles, G. G., Martin, N. T., Andrian, I. J. *Anesthesiology*, 1956, 17, 213
Miller, A. J., Baker, L. A. *Arch. Intern. Med.*, 1952, 89, 591
Miller, W. S., Woods, W. W. *Brit. Heart J.*, 1943, 5, 101
Mills, D.C.B., Robb, I. A., Roberts, G.C.K. *J. Physiol.*, 1968, 195, 715
Mingazetdinova, L. N. In: *Epidemiologiya arterialnoi gipertonii i koronarnogo ateroskleroza* (Epidemiology of Arterial Hypertension and Coronary Atherosclerosis). Moscow, 1969, 2, 54
Mintz, S. S., Katz, L. N. *Arch. Intern. Med.*, 1947, 80, 205
Mironova, U. P. Ob aritmiyakh pri koronarnoi nedostatochnosti, ikh raspoznavanii i prognosticheskom znachenii (Concerning Arrhythmias in Coronary Failure. Their Diagnosis and Prognostic Significance). Diss. Voronezh, 1963
Mirrakhimov, M. M., Slavova, Ts. N. In: *Rasprostranenie gipertonicheskoi bolezni i koronarnogo ateroskleroza i usloviya zhizni* (Distribution of the Hypertensive Vascular Disease and Coronary Atherosclerosis, and the Conditions of Life). Moscow, 1964, 138
Mitchell, J. R., Parish, D. J. *Brit. Med. J.*, 1960, 5213, 1626
Mitin, K. S. Submikroskopicheskaya morfologiya serdtsa pri infarkte miokarda. Elektronnomikroskopicheskoe issledovanie serdtsa pri infarkte miokarda u cheloveka i v eksperimente (Submicroscopic Morphology of the Heart in Myocardial Infarction. Electron Microscopy of the Heart in Myocardial Infarction in Man and in Experiment). Diss. Moscow, 1969

Mittra, B. *Lancet*, 2, 1438
Moiseev, S. G. In: *Voprosy ostroi vnutrennei kliniki* (Problems of Acute Internal Clinic). Moscow, 1949, 21
Moiseev, S. G. *Klin. med.*, 1955, 10, 22
Moiseev, S. G. *Sov. med.*, 1956, 10, 19
Moiseev, S. G. *Sov. med.*, 1962, 6, 30
Moiseev, S. G., Akchurina, E. A., Novoselskaya, V. V. *Trudy Moskovskogo nauchno-issledovatelskogo instituta skoroi pomoshchi* (Transactions of the Moscow First-Aid Research Institute). Moscow, 1964, 10, 61
Moiseev, S. G., Filimonova, M. V. *Kardiol.*, 1969, 2, 3
Moiseev, S. G., Tinditnik, V. S. *Kardiol.*, 1967, 1, 25
Moiseev, S. G., Ustinova, E. Z. *Kardiol.*, 1967, 8, 98
More, B. M., Sommers, S. C. *Amer. Heart J.*, 1962, 64, 323
Moritz, A. R., Zamcheck, N. *Arch. Path.*, 1946, 42, 459
Morris, J. N. *Mod. Conc. Cardiov. Dis.*, 1960, 29, 625
Morris, J. N. *Mod. Conc. Cardiov. Dis.*, 1961, 30, 633
Morris, J. N., Crawford, M. D. *Brit. Med. J.*, 1958, 2, 1485
Morris, J. N., Heady, J. A. *Brit. J. Industr. Med.*, 1953, 10, 245
Morrison, L. M. *J.A.M.A.*, 1960, 173, 884
Moshkov, V. N. *Lechebnaya fizkultura v klinike nervnykh boleznei* (Exercise Therapy in the Clinic of Nervous Diseases). Moscow, 1959
Moyer, J. B., Hiller, G. I. *Amer. Heart J.*, 1951, 41, 340
Müller, A. *Cardiologia*, 1962, 40, 62
Mustard, J. F., Rowsell, H. C., Murphy, E. A. *et al. J. Clin. Invest.*, 1963, 42, 1783
Mustard, J. F., Murphy, E. A. *Brit. Med. J.*, 1963, 5334, 846
Mustard, J. F., Murphy, E. A., Rowsell, H. C. *et al. J. Atheroscler. Res.*, 1964, 4, 1
Myasnikov, A. L. *Kardiol.*, 1961, 1, 4
Myasnikov, A. L. *Ateroskleroz* (Atherosclerosis). Moscow, 1960
Myasnikov, A. L. *Kardiol.*, 1962, 1, 3
Myasnikov, A. L. *Kardiol.*, 1963, 4, 3
Myasnikov, A. L. *Gipertonicheskaya bolezn i ateroskleroz* (Hypertensive Vascular Disease and Atherosclerosis). Moscow, 1965
Myasnikov, A. L., Akhrem-Akhremovich, R. M., Kakurin, L. I. *et al.* In: *Aviatsionnaya i kosmicheskaya meditsina* (Aviation and Space Medicine). Moscow, 1963, 368
Myasnikov, L. A., Metelitsa, V. I., Grigorian, R. A. *et al. Kardiol.*, 1968, 11, 89
Myasnikov, L. A., Chazov, E. I., Skhvatsabaya, I. K., Kipshidze, N. N. *Eksperimentalnye nekrozy miokarda* (Experimental Myocardial Necroses). Moscow, 1963
Myers, G. B., Klein, H. A., Hiratzka, T. *Amer. Heart J.*, 1948, 36, 838
Myers, G. B., Klein, H. A., Hiratzka, T. *Amer. Heart J.*, 1949, 38, 547
Myers, G. B., Klein, H. A., Stofer, B. E. *Amer. Heart J.*, 1948, 36, 535
Myers, G. B., Klein, H. A., Stofer, B. E. *Amer. Heart J.*, 1949, 37, 374
Myers, G. B., Klein, H. A., Hiratzka, T. *Amer. Heart J.*, 1949, 37, 205
Naddachina, T. A. Patologicheskaya anatomiya venechnykh arterii serdtsa pri skoropostizhnoi smerti ot ostroi koronarnoi nedostatochnosti i voprosy tanatogeneza (Pathological Anatomy of the Coronary Arteries in Sudden Death from Acute Coronary Failure, and Problems of Thanatogenesis). Diss. Moscow, 1961
Naegeli, T. *Med. Welt.*, 1960, 3, 154
Naumann, W. *Dtsch. Arch. Klin. Med.*, 1974, 193, 33
Nayler, W. G., McInnes, I., Swann, J. B. *et al. Amer. Heart J.*, 1967, 73, 207
Nazarova, T. A. Tezisy dokladov 3-i nauchnoi konferentsii Semipalatinskogo meditsinskogo instituta (Theses of Reports to the Third Scientific Conference of the Semipalatinsk Medical Institute). Semipalatinsk, 1959, 16
Nedlina, E. M. *Klin. med.*, 1964, 3, 124

Nedlina, E. M., Komrakova, A. M., Beloborodov, R. A. *Klin. med.*, 1962, 5, 141
Nekrasova, A. A. *Ter. arkh.*, 1962, 4, 22
Nelson, A. M. *Northw. Med.* (Seattle). 1956, 55, 643
Nesterov, V. S. *Ter. arkh.*, 1954, 1, 73
Nesterov, V. S. *Klin. med.*, 1958, 1, 49
Nesterov, V. S., Kochetov, A. M., Dikareva, Y. A. *Anevrizma serdtsa* (Cardiac Aneurysm). Moscow, 1963
Nesvadba, P. *Cardiologia*, 1955, 26, 103
Newman, M. *Lancet*, 1951, 6663, 1045
Nezlin, V. E. *Narusheniya venechnogo krovoobrashcheniya* (Disturbances in Coronary Circulation). Moscow, 1956
Nezlin, V. E., Dolgoplosk, N. A. *Ter. arkh.*, 1949, 5, 62
Nezlin, V. E., Karpai, S. E. *Analiz i klinicheskaya otsenka elektrokardiogrammy* (Analysis and Clinical Evaluation of the Electrocardiogram). Moscow, 1959
Nickerson, M., Karr, G. W., Dressel, P. E. *Circulat. Res.*, 1961, 9, 209
Nicolaysen, R. *Proc. Roy. Soc. Biol.*, 1962, 156, 365
Nielsen, B. L., Jörgensen, F. S. *Acta Med. Scand.*, 1966, 180, 631
Nikitin, U. P. Svyortyvayushchie, protivosvyortyvayushchie i fibrinoliticheskie svoistva stenki aorty v norme i pri ateroskleroze (Coagulative, Anticoagulative and Fibrinolytic Properties of the Aorta in Health and in Atherosclerosis). Diss. Novokuznetsk, 1967
Nikolaev, M. P. *Uchebnik farmakologii* (Textbook of Pharmacology). Moscow, 1948
Nikolaeva, L. F. *Kardiol.*, 1961, 1, 51
Nikolaeva, L. F. Izmenenie soderzhaniya geparina v krovi bolnykh aterosklerozom i infarktom miokarda (Change in the Heparin Content of the Blood in Atherosclerosis and Myocardial Infarction Patients). Diss. Moscow, 1962
Novikov, A. T. *Klin. med.*, 1954, 5, 67
Novikov, A. T., Kuzmina, H. I. *Klin. med.*, 1963, 10, 38
Novikova, K. F. *Sbornik rabot Sverdlovskogo meditsinskogo instituta* (Collection of Articles of the Sverdlovsk Medical Institute). Sverdlovsk, 1965, 45, 87
Novikova, E. B. *Fiziol. zh. SSSR*, 1967, 10, 1145
Novikova, K. F., Kapinos, V. F., Fialko, V. A. *et al.* In: *Stenokardiya i infarkt miokarda. Trudy fakultetskoi terapevticheskoi kliniki Sverdlovskogo meditsinskogo instituta* (Angina Pectoris and Myocardial Infarction. Transactions of the Faculty Therapeutic Clinic of the Sverdlovsk Medical Institute). Sverdlovsk, 1965, Vol. 45, 94
Nussbaum, A. *Arch. Mikr. Anat.*, 1912, 80, 450
Nydick, I., Ruegsegger, P., Wroblewski, F. *et al. Circulation*, 1957, 15, 324
Oblath, R. W., Levinson, D. C., Griffith, G. C. *J.A.M.A.*, 1952, 149, 1276
Oborina, Y. N. Antitrombinovaya (geparinovaya) aktivnost krovi i stenki aorty pri ateroskleroze (Antithrombin [Heparin] Activity of the Blood and Wall of the Aorta in Atherosclerosis). Diss. Novokuznetsk, 1967
Obraztsov, V. P., Strazhesko, N. D. *Klin. med.*, 1949, 11, 15
Ognev, B. V., Savvin, V. N., Savelieva, L. A. *Krovenosnye sosudy serdtsa v norme i patologii* (The Cardiac Blood Vessels in Health and Disease). Moscow, 1954
Oliver, R. M. *Brit. J. Industr. Med.*, 1967, 24, 181
Opaleva-Stegantseva, V. A., Litvintseva, G. A., Duberg, A. V. *et al. Tezisy dokladov 4-go soveshchaniya po epidemiologii gipertonicheskoi bolezni i koronarnogo ateroskleroza* (Theses of Reports to the Fourth Conference on the Epidemiology of the Hypertensive Vascular Disease and Coronary Atherosclerosis). Moscow, 1965, 10
Oppel, V. A. *Arkh. path. anat.*, 1901, 164, 406
Oram, S., Davies, J. P., Weinbren, J. *Lancet*, 1963, 2, 159
Oram, S., Sowton, E. *Brit. Med. J.*, 1963, 5363, 949
Orbeli, L. A. *Fiziol. zh. SSSR*, 1936, 5-6, 728
Orlov, V. N., Avrukh, R. L. *Trudy Tsentralnogo instituta usovershenstvovaniya*

vrachei (Transactions of the Central Institute of Postgraduate Medical Training). Moscow, 1964, Vol. 70, 80
Osher, H. L., Wolff, L. *Amer. Heart J.*, 1953, 45, 429
Ostapyuk, F. Y. *Uchonye zapiski Instituta farmakologii i khimioterapii AMN SSSR* (Transactions of the Institute of Pharmacology and Chemotherapy, USSR Academy of Medical Sciences). Moscow, 1960, Vol. 2, p. 265
Ostapyuk, F. Y. Infarkt miokarda (Voprosy kliniki, elektrokardiograficheskoi diagnostiki i lecheniya). (Myocardial Infarction. Problems of the Clinic, Electrocardiographic Diagnosis and Treatment). Diss. Moscow, 1965
Ostrander, L. D., Brandt, R. L., Kjelsberg, M. O. *et al. Circulation*, 1965, 31, 888
Ostrander, L. D., Francis, T., Hayner, N. S. *et al. Ann. Intern. Med.*, 1965, 62, 1188
Owren, P. A. *Thrombos. Diathes. Haemorrh.*, 1958, 2, 492
Ozarai, A. I. Sostoyanie tebezievykh sosudov v razlichnykh usloviyakh bolezneno izmenennogo miokarda (State of the Thebesian Vessels under Different Conditions of the Morbidly Affected Myocardium). Diss. Moscow, 1956
Panchenko, V. M. *Ter. arkh.*, 1956, 7, 10
Panchenko, V. M. *Ter. arkh.*, 1962, 10, 40
Panchenko, V. M. *Ter. arkh.*, 1964, 4, 64
Panchenko, V. M., Andreenko, G. V. *Ter. arkh.*, 1964, 1, 43
Panfilov, U. A. O tromboendokardite pri infarkte miokarda (Concerning Thromboendocarditis in Myocardial Infarction). Diss. Kuibyshev, 1961
Panfilov, U. A. In: *Kompensatorno-prisposobitelnye protsessy* (Compensatory-Adaptive Processes). Kuibyshev, 1961, 100
Pardee, H.E.B. *Arch. Intern. Med.*, 1920, 26, 244
Pardee, H.E.B. *Amer. J. Med. Sci.*, 1925, 169, 270
Parin, V. V. In: *Sovremennye problemy kardiologii* (Modern Problems of Cardiology). Moscow, 1960, 27
Parin, V. V., Fedorov, B. M. In: *Nedostatochnost serdtsa i aritmii.* Leningrad, 1966, 182
Parkinson, J., Bedford, D. E. *Heart*, 1927, 14, 195
Parno, A. I. *Materialy konferentsii doktorantov, aspirantov i ordinatorov Kishinevskogo meditsinskogo instituta* (Proceedings of the Conference of Postgraduate Students and Interns of the Kishinev Medical Institute). Kishinev, 1965, 100
Paterson, J. C. *J. Occup. Med.*, 1961, 3, 59
Paul, J. R. *Clinical Epidemiology.* Chicago, 1966
Paul, M. H., Norman, L. R., Zoll, P. M. *et al. Circulation*, 1957, 16, 608
Paul, O., Lepper, M. H., Phelan, W. H. *et al. Circulation*, 1963, 28, 20
Pell, S., d'Alonzo, C. A. *J.A.M.A.*, 1963, 185, 831
Pentecost, B. L., Mayne, N. M., Lamb, P. *Lancet*, 1968, 1, 7549, 946
Pepler, W. J., Meyer, B. J. *Arch. Path.*, 1961, 71, 209
Perlik, E. *Antikoagulantien.* Leipzig, 1964
Petersen, V. R. *Acta med. Scand.*, 1959, 164, 131
Petrov, B. A., Lobachev, S. V. *Vestn. khir.*, 1956, 10, 35
Petrov, I. P. *Travmaticheskii shok* (Traumatic Shock). Moscow, 1962
Petrov, I. P., Vasadze, G. Sh. *Neobratimye izmeneniya pri shoke i krovopotere* (Irreversible Changes in Shock and Blood Loss). Leningrad, 1966
Petrovsky, B. V. *Vestn. khir.*, 1960, 9, 11
Petrovsky, B. V. *Kardiol.*, 1961, 1, 23
Petrovsky, B. V., Efuni, S. N. *Trudy 2-i Vsesoyuznoi konferentsii khirurgov, travmatologov i anesteziologov* (Transactions of the Second All-Union Conference of Surgeons, Traumatologists and Anaesthesiologists). Moscow, 1963, 268
Petrovsky, B. V., Efuni, S. N. *Lechebny narkoz* (Therapeutic Anaesthesia). Moscow, 1967
Petrovsky, B. V., Kozlov, I. Z. *Anevrizmy serdtsa* (Cardiac Aneurysms). Moscow, 1965
Pevzner, I. Ya. Infarkt predserdii (Atrial Infarction). Diss. Saratov, 1962
Pevzner, I. Ya Gormony nadpochechnikov i ostraya koronarnaya nedostato-

chnost (Adrenal Hormones and Acute Coronary Failure). Diss. Kuibyshev, 1969
Phares, W. S., Edwards, J. E., Burchell, H. B. *Proc. Mayo Clin.*, 1953, 28, 264
Pickering, G. W. *J.A.M.A.*, 1948, 137, 423
Pirogov, N. I. *Nachala obshchei voenno-polevoi khirurgii, vzyatye iz nablyudenii voyenno-gospitalnoi praktiki i vospominanii o krymskoi voine i kavkazskoi ekspeditsii* (Principles of General Battlefield Surgery Taken from Observations of Military Hospital Practice and Recollections of the Crimean War and the Caucasian Expedition). Moscow-Leningrad, 1941
Pisha, E., Gammer, Ya. *Pat. fiziol.*, 1963, 4, 17
Pitt, B. *Circulation*, 1959, 20, 816
Pletitsyn, D. F., Averiyanova, L. L. *Vestn. AMN SSSR*, 1967, 2, 19
Pletnev, D. D. *Bolezni serdtsa* (Diseases of the Heart). Moscow-Leningrad, 1936
Plotz, M. *Coronary Disease.* Moscow, 1961
Podonenko, A. I. *Vestn. khir.*, 1961, 5, 128
Poe, N. D., Swanson, L. A., Dore, E. K. *et al. Amer. Heart J.*, 1967, 73, 582
Polezhaev, L. V., Akhabadze, L. V., Zakharova, N. A. *Dokl. AN SSSR*, 1958, 119, 5, 1039; 1961, 138, 3, 714
Polezhaev, L. V., Akhabadze, L. V., Muzlaeva, N. A. *et al. Stimulyatsiya regeneratsii myshtsy serdtsa* (Stimulation of Regeneration of the Heart Muscle). Moscow, 1965
Pollard, J. W., Hamilton, M. J., Christensen, N. A. *et al. Circulation*, 1962, 25, 311
Poller, L. J. *Clin. Path.*, 1957, 10, 348
Popov, V. G. In: *Voprosy patologii i fiziologii serdtsa* (Problems of Pathology and Physiology of the Heart). Moscow, 1955, 83, 85
Popov, V. G. Povtornye infarkty miokarda (Recurrent Myocardial Infarctions). Diss. Moscow, 1964
Popov, V. G., Gvatua, N. A. *Ter. arkh.*, 1957, 3, 51
Pozdyunina, N. M. Izmeneniya aktivnosti fermentov i soderzhaniya elektrolitov v miokarde pri ego gipertrofii i nedostatochnosti v eksperimente (Changes in the Activity of Enzymes and the Content of Electrolytes in the Myocardium in Experimental Myocardial Hypertrophy and Failure). Diss. Moscow, 1967
Presnyakov, D. F. *Kardiol.*, 1962, 6, 43
Preston, J. A., Batsakis, J. G., Brierl, R. O. *et al. Amer. J. Clin. Path.*, 1965, 44, 71
Prinzmetal, M., Bergman, H. C., Kruger, H. *et al. Amer. Heart J.*, 1948, 35, 689
Prinzmetal, M., Ekneckt, A., Toyoshima, H. *et al. Amer. J. Cardiol.*, 1959, 3, 276
Prinzmetal, M., Kayland, S., Margoles, G. *et al. J. Mount Sinai Hosp.*, 1942, 8, 933
Prinzmetal, M., Kennamer, R., Shaw, C. *et al. Circulation*, 1953, 7, 1
Prinzmetal, M., Massumi, R. *J.A.M.A.*, 1955, 159, 177
Prinzmetal, M., Shaw, C., Maxwell, M. *et al. Amer. J. Med.*, 1954, 16, 469
Prinzmetal, M., Simkin, B., Bergman, H. C. *et al. Amer. Heart J.*, 1947, 33 420
Prinzmetal, M., Toyoshima, H., Ekmekci, A. *et al. Amer. J. Cardiol.*, 1961, 8, 493
Prinzmetal, M., Weiner, S. M., Bhuyan, M. C. *Amer. J. Cardiol.*, 1958, 1, 26
Pribylova, L. P., Korsunsky, A. A., Spiridonov, Y. V. *et al. Materialy dokladov 7-go soveshchaniya po epidemiologii ishemicheskoi bolezni serdtsa, ateroskleroza i gipertonicheskoi bolezni* (Proceedings of the Seventh Conference on the Epidemiology of Ischaemic Heart Disease, Atherosclerosis and the Hypertensive Vascular Disease). Moscow, 1969, 17
Prikazchikov, A. I., Petrova, V. M. *Klin. med.*, 1954, 1, 62
Probatova, N. A. Zhirovaya distrofiya miokarda v svete sovremennykh dannykh (Fatty Dystrophy of the Myocardium in the Light of Present-Day Data). Diss. Moscow, 1965
Provenza, D. V., Scherlis, S. *Circulation*, 1959, 20, 35

Pruitt, R. D., Klakeg, C. H., Chapin, L. E. *Circulation*, 1955, 11, 517
Pushkar, U. T., Mukharlyamov, N. M., Chazov, E. I. In: *Ateroskleroz i Tromboz* (Atherosclerosis and Thrombosis). Moscow, 1964, 189
Raab, W. Prevention of Ischaemic Heart Disease. Springfield, 1966
Raab, W., Chaplin, J. P., Bajusz, E. *Proc. Soc. Exp. Biol.*, 1964, 116, 605
Rabson, S. M., Helpern, M. *Amer. Heart J.*, 1948, 35, 635
Radushkevich, V. P., Afanasiev, N. A., Pozdnyakov, G. P. In: *Elektronika i khimiya v kardiologii* (Electronics and Chemistry in Cardiology). Voronezh, 1964, 359
Radushkevich, V. P., Afanasiev, N. A., Pozdnyakov, G. P. In: *Voprosy reanimatsii, anesteziologii, neprokhodimosti kishechnika, travmy kosti* (Problems of Resuscitation, Anaesthesiology, Intestinal Obstruction, Bone Trauma). Voronezh, 1966, 68
Raevskaya, G. A. *Ter. arkh.*, 1948, 3, 44
Raevskaya, G. A. *Sov. med.*, 1948, 5, 10
Raevskaya, G. A. Infarkt miokarda (osobennosti techeniya, tromboembolicheskie oslozhneniya) (Myocardial Infarction. Peculiarities of Its Course, Thromboembolic Complications). Diss. Moscow, 1955
Raevskaya, G. A. In: *Voprosy serdechno-sosudistoi patologii* (Problems of Cardiovascular Pathology). Moscow, 1958, 123
Raevskaya, G. A. *Tromboembolicheskie oslozhneniya u bolnykh infarktom miokarda* (Thromboembolic Complications in Myocardial Infarction Patients). Moscow, 1960
Raevskaya, G. A. *Kardiol.*, 1964, 4, 37
Raevskaya, G. A., Kazmina, P. V. *Sov. med.*, 1962, 3, 24
Raiskina, M. E. *Kardiol.*, 1967, 8, 3
Raiskina, M. E., Onishchenko, N. A., Feld, B. N. In: *Aktualnye problemy serdechno-sosudistoi patologii.* (Urgent Problems of Cardiovascular Pathology). Moscow, 1967, 283
Raiskina, M. E., Khodas, M. Ya., Samoilova, Z. T. *Kardiol.*, 1963, 4, 45
Raiskina, M. E., Samoilova, Z. T., Khodas, M. Ya. *Pat. fiziol. i eksper. ter.*, 1963, 2, 19
Rapoport, Ya. L. *Arkh. pat. anat. i pat. fiziol.*, 1935, 1, 66
Ratner, N. A., Spivak, G. L. *Ter. arkh.*, 1960, 9, 20
Ravin, A., Geever, E. F. *Arch. Intern. Med.*, 1946, 78, 125
Reaven, G., Calciano, A. J., Cody, R. M. *et al. Circulation*, 1962, 26, 775
Regan, T. J., Frank, M. J., McGinty, J. F. *et al. Circulation*, 1961, 23, 365
Reicherzt, P. L., Noell, G., Hemmati, A. *Med. Welt*, 1967, 38, 2236
Reitmann, N., Greenwood, W. R., Kler, J. H. *Amer. J. Med. Sci.*, 1942, 203, 792
Research Committee. *Lancet*, 1965, Sept., 11, 501
Richter, W., Imdahl, H. *Med. Welt*, 1962, 16, 842
Rinzler, S.H., Travell, J., Karp, D., Charlson, D. *Amer. J. Physiol.*, 1956, 184, 605
Robledo, M. *Amer. J. Path.*, 1956, 32, 1215
Roine, P. *Proc. 4th Intern. Diet. Congr.*, 1965, 105
Romanov, U.D. *Klin. med.*, 1963, 10, 32
Romanova, Y. M. In: *Voprosy kardiologii* (Problems of Cardiology). Moscow, 1964, 63
Rose, G. *Brit. J. Prev. Soc. Med.*, 1964, 18, 75
Rose, G. A., Thomson, W. B., Williams, R. T. *Brit. Med. J.*, 1965, 544, 1531
Rosenbaum, F. F., Levine, S. A. *Arch. Intern. Med.*, 1941, 68, 913
Rosenman, R. H., Friedman, M., Jenkins, C. D. *et al. J.A.M.A.*, 1966, 198, 1159
Rothfield, E. L., Bernstein, A., Wachtel, F. *et al. Amer. J. Cardiol.*, 1961, 7, 496
Rothfield, E. L., Wachtel, F. W., Karlen, W. S. *et al. Circulation*, 1959, 20, 759
Roubelakis, G., Grosgogeat, Y., Lenegre, J. *Arch. Mal. Coeur.*, 1965, 58, 1420
Roubelakis, G., Grosgogeat, Y., Lenegre, J. *Arch. Mal. Coeur.*, 1966, 59, 391

Rowe, G. G., Chlius, C. J., Afonso, S. *et al. J. Clin. Invest.*, 1961, 40, 1217
Royston, G. R. *Angiology*, 1967, 18, 133
Rubanovsky, B. R. *Kardiol.*, 1961, 5, 81
Ruda, M. Y. *Trudy Nauchno-issledovatelskogo instituta eksperimentalnoi i klinicheskoi terapii Ministerstva zdravookhraneniya Gruzinskoi SSR* (Transactions of the Research Institute of Experimental and Clinical Therapy of the Ministry of Health of the Georgian SSR). Tbilisi, 1967, Vol. 3, p. 421
Rudneva, O. B. *Sov. med.*, 1965, 11, 83
Ruegsegger, P., Nydick, I., Abarquez, R. *et al. Amer. J. Cardiol.*, 1960, 6, 519
Rumyantsev, P. P. Eksperimentalno-gistologicheskoe issledovanie serdechnoi myshtsy koshki v vozrastnom razreze (Experimental Histological Study of the Cat's Heart Muscle in Its Developmental Stages). Diss. Leningrad, 1953
Rushmer, R. F. *Circulation*. 1960, 21, 744
Rushmer, R. F. *Cardiovascular Dynamics*. Philadelphia, 1961
Russek, H. I., Zohman, B. L. *Amer. J. Med. Sci.*, 1954, 228, 133
Russel, R. A., Crafoord, J., Harris, A. S. *Amer. J. Physiol.*, 1961, 200, 995
Ryazhenov, V. V. *Farmakol. i toksikol.*, 1963, 4, 501
Sabelli, H. C. *C.R. Soc. Biol.*, 1961, 155, 155
Sadove, M. S., Levin, M. J., Rose, R. F. *J.A.M.A.*, 1954, 155, 626
Sager, R. V. *Arch. Intern. Med.*, 1934, 53, 140
Salmanovich, V. S. In: *Ateroskleroz i infarkt miokarda* (Atherosclerosis and Myocardial Infarction). Moscow, 1959, 266
Salmanovich, V. S. *Kardiol.*, 1961, 6, 18
Salmanovich, V. S., Udelnov, M. G. In: Voprosy patologii i fiziologii serdtsa (Problems of Pathology and Physiology of the Heart). Moscow, 1955, 75
Samoilova, Z. I. *Farmakol. i toksikol.*, 1960, 6, 503
Samoilova, Z. T., Ryazhenov, V. V. *Farmakol. i toksikol.*, 1961, 1, 66
Sanders, R. J., Kern, W. H., Blount, S. G. *Amer. Heart J.*, 1956, 51, 736
Sanders, R. J., Neuberger, K. T., Ravin, A. *Dis. Chest*, 1957, 31, 316
Saphir, O., Ohringer, L., Wong, R. *Arch. Path.*, 1956, 62, 159
Saphir, O., Priest, W. S., Hamburger, W. W. *et al. Amer. Heart J.*, 1935, 10, 765
Sarnoff, S. J., Braunwald, E., Welch, G. H. *et al. Amer. J. Physiol.*, 1958, 192, 148
Sasahara, A. A., Sidd, J. J., Tremblay, G. *et al.* In: *Progr. in Cardiovacs. Dis.*, 1966, 9, 3, 269
Saveliev, V. S., Kostenko, I. G., Savchuk, B. D. *Blokada serdtsa* (*Heart Block*). Moscow, 1967
Savenko, P. N. Cited in: I. K. Akhunbaev *et al.*
Sawyer, P. N., Pate, J. W., Weldon, C. S. *Amer. J. Physiol.*, 1953, 175, 108
Schamroth, L. *Amer. J. Cardiol.*, 1966, 18, 438
Scheidler, K. Z. *Ärztl. Fortbild.*, 1963, 57, 1099
Schenk, W. G., Menno, A. D., Martin, J. W. *Ann. Surg.*, 1961, 154, 295
Scherlis, L., Grishman, A., Sandberg, A. A. *Amer. Heart J.*, 1951, 42, 24
Schert, D., Boyd, L. *J. Klinik und Therapie der Herzkrankheiten und der Gefässerkrankungen*. Wien, 1955
Schimert, G., Schimmler, W., Schwalb, H. *et al.* In: G. Bergmann *Handbuch der inneren Medizin*. Berlin, 1960, Bd. 9, T.3, S. 653
Schlappi, J. C., Landale, D. G. *Amer. Heart J.*, 1954, 47, 432
Schlesinger, M. J. *Amer. Heart J.*, 1938, 15, 528
Schlicher, J., Hellerstein, H. K., Katz, L. N. *Medicine*, 1954, 33, 43
Schmidt, E. V., Ustinova, E. Z., Drigo, E. F. *Klin. med.*, 1963, 9, 13
Schnur, S. *J.A.M.A.*, 1954, 156, 1127
Schoenmackers, J. Z. *Kreisl.-Forsch.*, 1950, 39, 68
Schoenmackers, J., Vieten, H. *Atlas postmortalez Angiogramme*. Stuttgart, 1954
Schoenmackers, J. In: *Probleme der Coronardurchblutung*. Berlin, 1958
Schoenmackers, J., Vieten, H. *Dtsch. med. Wschr.*, 1954, 79, 671
Schpalteholz, W. *Die Arterien der Herzwand*. Leipzig, 1924

Schrade, W., Bohle, E., Biegler, R. *Lancet*, 1960, 2, 1409
Schröder, R., Dissmann, W., Buschmann, H. J. *et al. Dtsch. med. Wschr.*, 1966, 45, 2022
Schröder, R., Dissmann, W., Buschmann, H. J. *et al. Ztschz. Kreisl. Forsch.*, 1967, 56, 1
Schürger, R. *Med. Welt*, 1968, 1, 58
Selye, H. *Necrotic Cardiopathy.* Moscow, 1961
Sedov, K. R. Epidemiologiya i patologiya koronarnogo ateroskleroza v Irkutskoi oblasti (Epidemiology and Pathology of Coronary Atherosclerosis in Irkutsk Region). Diss. Moscow, 1966
Sedov, K. R. In: *Epidemiologiya arterialnoi gipertonii i koronarnogo ateroskleroza* (Epidemiology of Arterial Hypertension and Coronary Atherosclerosis). Moscow, 1966, Vol. 2, p. 46
Selavri, T. V. *Farmakol. i toksikol.*, 1958, 6, 43
Selye, H. *The Story of the Adaptation Syndrome.* Montreal, 1952
Selye, H. In: *Current Problems of Cardiovascular Pathology*, 1967, 127
Selzer, A. *Amer. Heart J.*, 1952, 44, 12
Semenov, E. P. Autoimmunnye protsessy pri infarkte miokarda (Auto-immune Processes in Myocardial Infarction). Diss. Simferopol, 1964
Semenovich, N. I. Kliniko-immunologicheskie paralleli pri ishemicheskoi bolezni serdtsa (Clinical and Immunological Parallels in the Ischaemic Heart Disease). Diss. Moscow, 1969
Sergeev, A. V. *Sov. med.*, 1954, 6, 13
Shakhbazian, E. S. Eksperimentalnye materialy po voprosu o narushenii venechnogo krovoobrashcheniya v serdtse (Experimental Data on the Problem of Disturbances in Coronary Circulation). Diss. Moscow-Leningrad, 1940
Shamesova, L. G. *Trudy Vsesoyuznoi conferentsii patologoanatomov.* (Transactions of the All-Union Conference of Pathoanatomists). Moscow, 1956, 266
Shamesova, L. G. In: *Nauchnye trudy Moskovskoi gorodskoi bolnitsy imeni S.P. Botkina* (Transactions of the S. P. Botkin Moscow City Hospital). Moscow, 1956, 61
Shamov, I. A. *Vrach. delo*, 1961, 4, 126
Shapiro, M. R., Cardenas, N. L., Sanchez, A. G. *Arch. Inst. Cardiol. Mex.*, 1967, 37, 352
Shapiro, R. L., Olivetti, R. G. *Circulation*, 1964, 30, 425
Shapiro, S., Weinblatt, E., Frank, C. W. *et al. J. Chron. Dis.*, 1965, 18, 527
Shelagurov, A. A., Sokolov, E. I. *Klin. med.*, 1963, 10, 21
Shelagurov, A. A., Trushinsky, E. K. *Ter. arkh.*, 1963, 17
Shelagurov, A. A., Trushinsky, E. K. *Ter. arkh.*, 1965, 2, 3
Sherstnev, K. M. *Materialy dokladov 7-go soveshchaniya po epidemiologii ishemicheskoi bolezni serdtsa, ateroskleroza i gipertonicheskoi bolezni* (Proceedings of the Seventh Conference on Epidemiology of the Ischaemic Heart Disease, Atherosclerosis and Hypertensive Vascular Disease). Moscow, 1969, 6
Shestakov, S. V. *Klin. med.*, 1951, 2, 24
Shestakov, S. V. *Ter. arkh.*, 1957, 7, 32
Shestakov, S. V. *Kardiol.*, 1961, 3, 10
Shestakov, S. V. *Grudnaya zhaba i infarkt miokarda* (Angina Pectoris and Myocardial Infarction). Moscow, 1962
Shestakov, S. V. *Kardiol.*, 1962, 6, 14
Shipp, J. C., Sidel, V. W., Donaldson, R. M. *et al. New Engl. J. Med.*, 1959, 261, 222
Shishkin, S. S. *Povtornye infarkty miokarda* (Recurrent Myocardial Infarctions). Moscow, 1963
Shkhvatsabaya, I. K. Znachenie nervnogo faktora v proiskhozhdenii infarkta miokarda u cheloveka i eksperimentalnykh nekrozov serdechnoi myshtsy (Role of the Nervous Factor in the Origin of Myocardial Infarction in Man and in Experimental Necroses of the Heart Muscle). Diss. Moscow, 1965
Shkhvatsabaya, I. K., Myasnikov, L. A., Trubetskoi, A. V. In: *Profilaktika i lechenie koronarnoi i serdechnoi nedostatochnosti.* (Prevention and Treatment of Coronary and Heart Failure). Leningrad, 1967, 185

Shnitka, T. K., Nacklas, M. M. *Amer. J. Path.*, 1963, 42, 507
Shpirt, Ya. U. *Sbornik nauchnykh rabot 3-i terapevticheskoi kliniki Odesskogo meditsinskogo instituta* (Collection of Scientific Articles of the Third Therapeutic Clinic of the Odessa Medical Institute). Odessa, 1935, 79
Shvarts, L. S. *Sov. med.*, 1944, 10-11, 24
Sibley, G. W., Mohler, S. R., Jones, N. W. *et al. Amer. J. Physiol.*, 1952, 171, 768
Sidorenko, B. A., *Ter. arkh.*, 1966, 7, 72
Sidorovich, S. Kh., Shanina, V. A. *Klin. med.*, 1961, 7, 86
Sievers, J., Blomqvist, G., Biorck, G. *Acta med. Scand.*, 1961, 169, 95
Sigal, A. M. *Naperstyanka i ee terapevticheskoe primenenie* (Digitalis and Its Therapeutic Use). Moscow, 1956
Sigler, L. H. *Arch. Intern. Med.*, 1954, 94, 341
Sinitsyn, N. P. *Grudn. khir.*, 1959, 4, 15
Sinitsyn, N. P. *Materialy 3-i konferentsii po voprosam regeneratsii i kletochnogo razmnozheniya* (Proceedings of the Third Conference on Problems of Regeneration and Cell Reproduction). Moscow, 1962, 151
Siterman, L. Ya. *Infarkt miokarda* (Myocardial Infarction). Minsk, 1938
Sivkov, I. I., Kukes, V. G., Sokolov, B. P. In: *Voprosy kardiologii i gastroenterologii* (Problems of Cardiology and Gastroenterology). Moscow, 1965, Vol. 3, p. 10
Skuba, N. D. *Arkh. pat.*, 1968, 9, 23
Skvortsov, V. I. *Kurs farmakologii* (A Course in Pharmacology). Moscow, 1948
Slapak, L. *Cardiologia*, 1953, 22, 228
Sloman, G., Stannard, M., Goble, A. *Amer. Heart J.*, 1968, 75, 140
Slutsky, M. E., Vysoky, F. F., Khvoinitskaya, I. L. *Ter. arkh.*, 1966, 12, 42
Smagin, G. A., Kasalitsa, Ch. L., Onikienko, B. A. In: *Gipertonicheskaya bolezn, ateroskleroz, koronarnaya nedostatochnost* (Hypertensive Vascular Disease, Atherosclerosis, Coronary Failure). Kiev, 1963, 278
Smetnev, A. S. Kardiogennyi shok pri infarkte miokarda. Patogenez, klinika i lechenie (Cardiogenic Shock in Myocardial Infarction. Pathogenesis, Clinical Aspects and Treatment). Diss. Moscow, 1966
Smetnev, A. S., Belkin, V. S., Tyufaeva, N. I. *Trudy 1-go Moskovskogo Meditsinskogo instituta* (Transactions of the First Moscow Medical Institute). Moscow, 1965, Vol. 36, p. 270
Smetnev, A. S., Kakhnovsky, I. M. *Klin. med.*, 1965, 3, 50
Smetnev, A. S., Kakhnovsky, I. M. *Trudy 1-go Moskovskogo meditsinskogo instituta* (Transactions of the First Moscow Medical Institute), 1965, Vol. 36, p. 107
Smirnov, V. N. *Kazansk. med. zh.*, 1962, 5, 9
Smirnov, V. N., Zhivotovskaya, I. L., Marchenko, L. A. *et al. Kazansk. med. zh.*, 1960, 4, 11
Smirnova, I. M. *Kazansk. med. zh.*, 1960, 5, 58
Smith, C. *J.A.M.A.*, 1953, 151, 167
Smolensky, V. S. *Bolezni aorty* (Diseases of the Aorta). Moscow, 1964
Smoliyannikov, A. V. *Trudy 14-go Vsesoyuznogo s''ezda terapevtov* (Transactions of the 14th All-Union Congress of Internists). Moscow, 1958, 305
Smoliyannikov, A. V., Apatenko, A. K. *Trudy Vsesoyuznoi konferentsii patologoanatomov* (Transactions of the All-Union Conference of Pathoanatomists). Moscow, 1956, 258
Smoliyannikov, A. V., Naddachina, T. A. *Voprosy patologicheskoi anatomii i patogeneza koronarnoi nedostatochnosti* (Problems of Pathological Anatomy and Pathogenesis of Coronary Failure). Moscow, 1963
Smoliyannikov, A. V., Naddachina, T. A. *Trudy 4-go Vsesoyuznogo s''ezda patologoanatomov* (Proceedings of the Fourth All-Union Congress of Pathoanatomists). Moscow, 1967, 112
Sodi-Pallares, D. *New Bases of Electrocardiography*. London, 1956
Sodi-Pallares, D., Medrano, G. A., De Micheli, A. *et al. Circulation*, 1961, 23, 836
Sodi-Pallares, D., Bisteni, A., Medrano, G. A. *et al. Dis. Chest*, 1963, 43, 424

Sodi-Pallares, D., Testelli, M. R., Fishleder, B. L. *et al. Amer. J. Cardiol.*, 1962, 9, 66
Sofieva, I. E. *Ter. arkh.*, 1965, 7, 81
Sokolov, P. A. *Vestn. rentgenol. i radiol.*, 1947, 5-6, 91
Soulier, J.-P. *Presse méd.*, 1957, 65, 66
Spain, D. M., Bradess, V. A. *Circulation*, 1960. 22, 239
Spain, D. M., Bradess, V. A., Irall P. *et al. Circulation*, 1963, 27, 12
Spain, D. M., Bradess, V. A., Victoria, A. *et al. Circulation*, 1961, 24, 1047
Spain, D. M., Nathan, D. J., Gellis, M. *Amer. J. Med. Sci.*, 1963, 245, 63
Spann, J. F., Moellering, R. C., Haber, E. *et al. New Engl. J. Med.*, 1964, 271, 427
Speransky, A. D. In: *Yazva zheludka i dvenadtsatiperstnoi kishki* (Gastric and Duodenal Ulcer). Moscow-Leningrad, 1935, 50
Speransky, N. I. *Klin. med.*, 1949, 3, 32
Staemmler, M., Wilhelms, P. *Medizinische*, 1953, 1639
Stamler, J. *Proc. Ann. Staff. Conf. Amer. Heart Ass.* New York, 1963
Starchevsky, V. S. *Materialy dokladov 7-go soveshchaniya po epidemiologii ishemicheskoi bolezni serdtsa, ateroskleroza i gipertonicheskoi bolezni* (Proceedings of the Seventh Conference on Epidemiology of the Ischaemic Heart Disease, Atherosclerosis and the Hypertensive Vascular Disease). Moscow, 1969, 26
Starkov, P. M. *Gazovyi narkoz* (Inhalation Anaesthesia). Moscow, 1950
Starobinets, K. M., Vetchinkina, N. A. *Ter. arkh.*, 1948, 6, 51
Stepanian, E. P., Tamarkina, E. D., Pospelov, E. P. *Kardiol.*, 1964, 4, 27
Stephenson, S. E., Younger, R., Scott, H. W. *J.A.M.A.*, 1962, 179, 46
Sternberg, M. *Das chronische partielle Herzaneuryzma.* Leipzig, 1914
Sternberg, N. H. In: *Atherosclerosis in Defined Population. Acta Pathol. et Microbiol. Scand.*, Suppl. 1968, 194, 34.
Sternby, N. *Acta path. microbiol. scand.*, 1968, Suppl. 194, 34, 182
Stevens, L. E., Burdette, W. J. *Arch. Surg.*, 1964, 88, 705
Stewart, C. F., Turner, K. B. *Amer. Heart J.*, 1938, 15, 232
Stokes, W. *Brit. Med. J.*, 1964, 5414, 910
Strasser, H. *Schweiz. med. Wschr.*, 1963, 93, 329
Straub, F. B. *Biochemistry.* Budapest, 1963
Straube, K. H. *Grundlagen für prophylaktische und metaphylaktische Massnahmen beim Herzinfarkt.* Leipzig, 1963
Strazhesko, N. D. *Izbrannye trudy* (Selected Works). Vols. 1-2, Kiev, 1955
Strukov, A. I. In: *Voprosy morfologii i patogeneza infarkta* (Problems of Morphology and Pathogenesis of Infarction). Moscow, 1959, 129
Strukov, A. I., Lushnikov, E. F., Gornak, K. A. *Gistokhimiya infarkta miokarda* (Histochemistry of Myocardial Infarction). Moscow, 1967
Strukov, A. I., Mitin, K. S. In *Sovremennye problemy fiziologii i patologii serdechno-sosudistoi sistemy* (Present-Day Problems of Physiology and Pathology of the Cardiovascular System). Moscow, 1967, 252
Stupnitsky, A. A. Kardialnaya astma. Voprosy kliniki, patogeneza, lecheniya (Cardiac Asthma. Problems of the Clinic, Pathogenesis and Treatment). Diss. Saratov, 1964
Sukhinin, P. L. In: *Voprosy skoroi meditsinskoi pomoshchi* (First Aid Problems). Moscow, 1963, 26
Sukhinin, P. L., Chuchkalov, V. P. *Sov. med.*, 1958, 10, 100
Sumarokov, A. V. Ektopicheskie aritmii v klinike vnutrennikh boleznei (Ectopic Arrhythmias in the Clinic of Internal Diseases). Diss. Moscow, 1965
Sumigoshi *et al. Acta med.*, 1965, 6
Sutton, D. C., Davis, M. D. *Arch. Intern. Med.*, 1931, 48, 1118
Swithinbank, J. M. *Brit. Heart J.*, 1954, 16, 562
Syme, J., Allan, W.S.A. *Brit. Heart J.*, 1951, 13, 352
Syrkin, A. L., Maevskaya, I. V. In: *Nedostatochnost serdtsa i aritmii* (Heart Failure and Arrhythmias). Leningrad, 1966, 287
Szirmai, E. Z. *Ges. Inn. Med.*, 1962, 17, 781
Szulc, E. J. *Przegl. lek.*, 1965, 21, 579

Tamarkina, A. D. *Ter. arkh.*, 1965, 6, 40
Tareev, E. M. In: *Trombozy i embolii* (Thromboses and Embolisms). Moscow, 1951, 114
Tartakovsky, M. B. *Odnopolyusnaya elektrokardiografiya* (Unipolar Electrocardiography). Leningrad, 1958
Teodori, M. I. *Ter. arkh.*, 1953, 1, 19
Teodori, M. I. *Klin. med.*, 1956, 9, 23
Terzian, H. *Sem. Hôp.*, 1954, 30, 838
Tetelbaum, A. G. *Klinicheskie tipy i formy stenokardii i nachala infarkta miokarda* (Clinical Types and Forms of Angina Pectoris and the Beginning of Myocardial Infarction). Moscow, 1960
Thomas, W. A., Kyu Taik Lee, Goodale, F. *et al.* In: *The Aetiology of Myocardial Infarction.* London, 1963, 153
Tochowicz, L., Pasyk, S., Denikiewicz, W. *Amer. Heart J.*, 1962, 63, 760
Tochowicz, L., Pasyk, S. *Cor et vasa*, 1965, 7, 185
Tokareva, A. M. *Kazansk. med. zh.*, 1959, 2, 26
Tokareva, A. M. *Trudy Kuibyshevskogo meditsinskogo instituta* (Transactions of the Kuibyshev Medical Institute). Kuibyshev, 1960, Vol. 13, p. 10
Tolgskaya, M. S. *Arkh. pat.*, 1946, 5-6, 43
Tolkacheva, N. I., Serebryakova, L. N. *Kazansk. med. zh.*, 1963, 2, 70
Tolubeeva, N. A. *Vrach. delo*, 1961, 4, 3
Toyoshima, H., Ekmekci, A., Flamm, E. *et al. Amer. J. Cardiol.*, 1964, 13, 498
Tranchesi, J., Teixeira, V., Ebaid, M. *et al. Amer. J. Cardiol.*, 1961, 7, 505
Tremblay, G. M., Sasahara, A. A. *Canad. Med. Ass. J.*, 1966, 95, 1066
Troshin, V. D. *Ter. arkh.*, 1961, 7, 35
Troshkin, V. D., Dvoretskaya, L. V. *Ter. arkh.*, 1964, 6, 24
Trubetskoi, A. V. In: *Ateroskleroz i koronarnaya nedostatochnost* (Atherosclerosis and Coronary Failure). Moscow, 1964, 24
Trubetskoi, A. V. In: *Samoregulyatsiya serdtsa* (Self-Regulation of the Heart). Moscow, 1967, 56
Trubetskoi, A. V., Novikova, E. B. In: *Ateroskleroz i koronarnaya nedostatochnost. Trudy ob''yedinyonnoi nauchnoi sessii Instituta kardiologii AMN SSSR* (Atherosclerosis and Coronary Failure. Transactions of the Unified Scientific Session of the USSR AMS Institute of Cardiology). Moscow, 1967, 290
Trushinsky, Z. K. *Kardiol.*, 1967, 1, 64
Tsukerman, B. M. In: *Nedostatochnost serdtsa i aritmii* (Heart Failure and Arrhythmias). Leningrad, 1966, 298
Tublin, I. N., Berman, L. B. *J.A.M.A.*, 1960, 174, 869
Tudhope, G. R., Donald, A. C. *Lancet*, 1954, 2, 465
Tulloch, J. A. *Brit. Heart J.*, 1952, 14, 379
Tumanovsky, M. N., Borodulin, Y. D., Nikitin, A. V. *et al. Kardiol.*, 1967, 1, 29
Tumanovsky, M. N., Borodulin, Y. D., Nikitin, A. V. *et al. Kardiol.*, 1968, 2, 21
Turner, P., Sowry, G. S. *Brit. J. Clin. Pract.*, 1964, 18, 13
Turpeinen, O., Karvonen, M. J., Roine, P. *6th Intern. Congr. Nutrition.* Edinburgh, 1963
Tviddiani, D. D., Dumbadze, Z. T. *Trudy nauchno-issledovatelskogo instituta eksperimentalnoi i klinicheskoi terapii Ministerstva zdravookhraneniya Gruzinskoi SSR* (Transactions of the Research Institute of Experimental and Clinical Therapy, Ministry of Health of the Georgian SSR). Tbilisi, 1963, Vol. 1, p. 127
Tynyanova, E. L., Bernshtein, G. I. *Kazansk. med. zh.*, 1966, 3, 22
Uchlinger, E. *Trudy 4-go Vsesoyuznogo s''ezda patologoanatomov* (Transactions of the Fourth All-Union Congress of Pathoanatomists). Moscow, 1967, 61
Udelnov, M. G. In: *Voprosy patologii i fiziologii serdtsa.* (Problems of Pathology and Physiology of the Heart). Moscow, 1955, 11

Udelnov, M. G. *Nervnaya regulyatsiya serdtsa* (Nervous Regulation of the Heart). Moscow, 1961
Udelnov, M. G. In: *Ateroskleroz i tromboz* (Atherosclerosis and Thrombosis). Moscow, 1964, 112
Underdahl, L. O., Smith, H. L. *Proc. Mayo Clin.*, 1947, 22, 479
Uzbekova, L. I. *Kazansk. med. zh.*, 1967, 1, 13
Vakhurkina, A. M. In: *Voprosy ostroi vnutrennei kliniki* (Problems of Acute Internal Clinic). Moscow, 1949, 67
Vasilenko, V. Kh., Melikova, M. U. *Klin. med.*, 1959, 2, 35
Vasilevskaya, F. M., Vakhromeeva, I. N. *Ter. arkh.*, 1965, 12, 81
Vastesaeger, M. M., Van der Straeten, P. P., Friart, J. *et al. Acta Cardiol.*, 1957, 12, 365
Verdun Di Cantogno, L., Chiche, P., Baillet, J. *Arch. Inst. Cardiol. Mex.*, 1959, 29, 65
Veselova, Y. A. *Bull. eksper. biol. i med.*, 1963, 10, 57
Videeva, V. I. *Kazansk. med. zh.*, 1965, 6, 46
Vikhert, A. M. In: *Myocardial Infarction. Proc. 9th Confer. Int. Soc. Georg. Pathology*. Leiden, 1966
Vikhert, A. M. Patologicheskaya anatomiya ostrogo gemorragicheskogo sindroma pri opukholyakh golovnogo mozga (Pathological Anatomy of Acute Haemorrhagic Syndrome in Cerebral Tumours). Diss. Moscow, 1969
Vikhert, A. M., Gudim, V. I., Boguslavsky, V. B. In: *Ateroskleroz i Tromboz* (Atherosclerosis and Thrombosis). Moscow, 1964, 101
Vikhert, A. M., Matova, E. E. In: *Serdechnaya i koronarnaya nedostatochnost* (Cardiac and Coronary Failure). Moscow, 1966, 247
Vikhert, A. M., Matova, E. E. In: *Aktualnye problemy serdechno-sosudistoi patologii* (Urgent Problems of Cardiovascular Pathology). Moscow, 1967. 290
Vikhert, A. M., Matova, E. E. *Trudy nauchno-issledovatelskogo instituta eksperimentalnoi i klinicheskoi terapii Ministerstva zdravookhraneniya Gruzinskoi SSR* (Transactions of the Research Institute of Experimental and Clinical Therapy, Ministry of Health of the Georgian SSR). Tbilisi, 1967, Vol. 3, p. 459
Vikhert, A. M., Matova, E. E. In: *Vzaimootnoshenie ateroskleroza i arterialnoi gipertonii. Trudy konferentsii* (Interrelation between Atherosclerosis and Arterial Hypertension. Conference Transactions). Moscow, 1968, 108
Vikhert, A. M., Sedov, K. P. *Kardiol.*, 1969, 5, 18
Vikhert, A. M., Ushkalov, A. F. *Arkh. pat.*, 1956, 1, 104
Vikhert, A. M., Zhdanov, V. S. *Kardiol.*, 1969, 9, 63
Vikhert, A. M., Zhdanov, V. S., Matova, E. E. *Vestn. AMN SSSR*, 1967, 4, 49
Vikhert, A. M., Zhdanov, V. S., Matova, E. E., Yagodovsky, V. S. *Trudy 4-go Vsesoyuznogo s''ezda patologoanatomov* (Transactions of the Fourth All-Union Conference of Pathoanatomists). Moscow, 1967, 334
Vilkovysky, A. L., Ostapyuk, F. E., Makarova, K. A. *Klin. med.*, 1965, 8, 62
Villem, G., Froneck, A., Ganz, B. In: *Trudy 14-go Vsesoyuznogo s''ezda terapevtov* (Proceedings of the 14th Congress of Internists). Moscow, 1958, 613
Villiger, U., Heyden, S. Z. *Kréisl.-Forsch.*, 1966, 55, 748
Villiger, U., Heyden-Stucky, S. *Schweiz. med. Wschr.*, 1966, 96, 748
Vinogradov, A. V. *Trudy 1-go Moskovskogo meditsinskogo instituta* (Transactions of the First Moscow Medical Institute). Moscow, 1956, Vol. 1, p. 148
Vinogradov, A. V. *Ter. arkh.*, 1957, 12, 20
Vinogradov, A. V. *Ter. arkh.*, 1959, 10, 3
Vinogradov, A. V. *Pat. fiziol. i eksper. ter.*, 1962 1, 15
Vinogradov, A. V. *Ostraya nedostatochnost krovoobrashcheniya pri infarkte miokarda* (Acute Circulatory Failure in Myocardial Infarction). Leningrad, 1965
Vinogradov, A. V., Sychova, I. M. *Kardiol.*, 1967, 2, 89
Vinogradov, A. V., Tsibekmakher, T. D., Matveev, L. N. *Kardiol.*, 1969, 9, 10

Vinogradov, V. N. *Ter. arkh.*, 1955, 7, 3
Vinogradov, V. N. *Ter. arkh.*, 1957, 7, 3
Vinogradov, V. N., Popov, V. G., Smetnev, A. S. *Ter. arkh.*, 1961, 10, 3
Vinogradov, V. N., Popov, V. G., Smetnev, A. S. *Ter. arkh.*, 1962, 3, 11
Vinogradov, V. N., Popov, V. G., Smetnev, A. S. *Kardiol.*, 1963, 4, 17
Vinogradov, V. N., Shapiro, L. B., Romodin, N. A. *Trudy 1-go Moskovskogo meditsinskogo instituta* (Transactions of the First Moscow Medical Institute). Moscow, 1965, Vol. 36, p. 5
Vinogradov, S. A. *Bull. eksper. biol. i med.*, 1956, 5, 27
Vinogradov, S. A. Eksperimentalnyi infarkt miokarda i vliyanie nekotorykh sostoyanii organizma na yego razvitie (Experimental Myocardial Infarction and the Influence of Some States of the Organism on Its Development). Diss. Moscow, 1957
Vinogradova, I. N. In: *Problemy sovremennoi neirokhirurgii* (Problems of Present-day Neurosurgery). Moscow, 1957, Vol. 2, p. 70
Vinogradova, O. N., Petrova, L. I., Sapozhnikova, M. A. *Ter. arkh.*, 1967, 4, 104
Vinogradsky, A. B., Usvatova, I. Ya. *Kardiol.*, 1964, 4, 31
Vinogradsky, O. V. *Kardiol.*, 1968, 8, 37
Vishnevsky, A. A., Tsukerman, B. M., Smelovsky, S. I. *Klin. med.*, 1959, 8, 26
Volkov, K. G. In: *Koronarnaya nedostatochnost* (Coronary Failure). Moscow, 1949, 1
Volkova, K. G. *Klin. med.*, 1956, 5, 12
Volynsky, Z. M. In: *Koronarnaya nedostatochnost* (Coronary Failure). Moscow, 1949, 32
Volynsky, Z. M., Gogin, E. E. *Zabolevaniya perikarda* (Diseases of the Pericardium). Leningrad, 1964
Volynsky, Z. M., Gordienko, Y. A. *Kardiol.*, 1967, 4, 12
Volynsky, Z. M., Isakov, I. I. *Klin. med.*, 1949, 12, 53
Votchal, B. Y. *Ocherk klinicheskoi farmakologii* (An Outline of Clinical Pharmacology). Moscow, 1963, 1965
Votchal, B. E., Averina, R. I. *Klin. med.*, 1962, 1, 15
Votchal, B. E., Vysoky, F. F. *Vengersk. med.*, 1966, 20, 19
Votchal, B. E., Magazanik, N. A. *Klin. med.*, 1959, 12, 37
Votchal, B. E., Slutsky, M. E. *Trudy 1-go Moskovskogo meditsinskogo instituta* (Transactions of the First Moscow Medical Institute). Moscow, 1967, Vol. 53, p. 251
Votchal, F. B., Grigorov, S. S. *Kardiol.*, 1968, 2, 123
Wade, W. *Brit. Heart J.*, 1959, 21, 545
Walker, W. J., Gregoratos, G. *Amer. J. Cardiol.*, 1967, 19, 339
Wang, C. H., Bland, E. F., White, P. D. *Ann. Intern. Med.*, 1948, 29, 601
Wartman, W. B. In: *Blood, Heart and Circulation.* 1940, 13, 122
Wartman, W. B. In: *Aetiology of Myocardial Infarction.* London, 1963, 115
Wartman, W., Hellerstein, H. *Ann. Intern. Med.*, 1948, 28, 41
Wartman, W. B., Jennings, R. B., Yokoyama, H. O. *et al. Arch. Path.*, 1956, 62, 318
Watson, W. C. *Brit. Med. J.*, 1963, 5369, 1366
Watts, D. T. *Ann. N.Y. Acad. Sci.*, 1960, 90, 74
Wearn, J. T. *J. Exp. Med.*, 1928, 47, 293
Weidmann, S. *J. Physiol.*, 1956, 132, 157
Weigert, C. *Arch. Path. Anat.*, 1880, 79, 87
Wennevold, A., Sandoe, E. *Acta med. Scand.*, 1966, 180, 715
Wessler, S., Gaston, L. W. *Circulation*, 1966, 34, 856
Wessler, S., Zoll, P. M., Schlesinger, M. J. *Circulation*, 1952, 6, 334
Westlund, K. *Bibl. Nutr. et Diet* (Basel), 1964, 6, 32
Whalen, W. J. *Circulat. Res.*, 1957, 5, 556
White, P. D. *Heart Disease.* New York, 1945
White, P. D., Donovan, H. *Hearts, Their Long Follow-Up.* Philadelphia, 1967
Wiggers, C. J. *Circulat. Res.*, 1954, 2, 271

Wiggers, C. J. *Ann. Intern. Med.*, 1945, 23, 158
Wiggers, C. J. *Amer. Heart J.*, 1947, 33, 633
Wiggers, C. J. *Circulation*, 1952, 5, 321
Wiggers, C. J. *Circulation Dynamics.* Moscow, 1957
Wikler, A. *Pharmacol. Rev.*, 1950, 2, 435
Wilens, S. L. *Science*, 1951, 114, 389
Wilson, F. N., Johnston, F. D., Hill, I. G. *et al. Trans. Ass. Amer. Phys.*, 1933, 48, 154
Wilson, F. N., Johnston, F. D., Hill, I. G. *et al. Proc. Soc. Exp. Biol.*, 1933, 30, 799
Wilson, F. N., McLeod, A. G., Johnston, F. D. *et al. Proc. Soc. Exp. Biol.*, 1933, 30, 797
Wilson, F. N., Rosenbaum, F. F., Johnston, F. D. *Adv. Intern. Med.*, 1947, 2, 1
Winbury, M. M., Green, D. M. *Amer. J. Physiol.*, 1952, 170, 555
Wissler, R. W., Eilert, M. L., Schroeder, M. A. *et al. Arch. Path.*, 1954, 57, 333
Witte, S., Bressel, D. *Folia haemat.*, 1958, 2, 236
Wolfson, S., Robbins, S. I., Krasnow, N. *Amer. Heart J.*, 1966, 72, 177
Wright, I. S., Marple, C. D., Beck, D. F. *Myocardial Infarction.* New York, 1954
Yakovlev, F. I. *Klin. med.*, 1927, 5, 19 (70), 1023
Yankevichute, Y. K. Razvitie i reparatsiya infarkta miokarda v zavisimosti ot rasprostranyennosti i vyrazhennosti stenoziruyushchego ateroskleroza venechnykh arterii serdtsa. Kliniko-morfologicheskie nablyudeniya (Development and Repair of Myocardial Infarction Depending on the Extent and Intensity of the Stenosing Coronary Atherosclerosis. Clinical and Morphological Findings). Diss. Kaunas, 1967
Yanushkevichus, Z. I. *Kardiol.*, 1970, 2, 35
Yanushkevichus, Z. I., Bluzhas, I. N. *Trudy 1-i Vsesoyuznoi kardiologicheskoi konferentsii* (Transactions of the First All-Union Cardiological Conference). Leningrad, 1964, 54
Yanushkevichus, Z. I., Bluzhas, I. N., Vitkus, A. S. In: *Serdechnaya i koronarnaya nedostatochnost* (Heart and Coronary Failure). Moscow, 1966, 217
Yanushkevichus, Z. I., Shnipas, P. A. *Kardiol.*, 1965, 6, 47
Yanushkevichus, Z. I., Shnipas, P. A. In: *Aktualnye problemy serdechno-sosudistoi patologii* (Urgent Problems of Cardiovascular Pathology). Moscow, 1967, 95
Yaroshevsky, A. Ya, Zhavoronkova, E. K. *Tezisy dokladov konferentsii po probleme ateroskleroza* (Theses of Reports to the Conference on the Problem of Atherosclerosis). Leningrad, 1962, 97
Yasakova, O. I. *Vrach. delo*, 1956, 12, 1237
Yasakova, O. I. Infarkt miokarda. Vozrastnye osobennosti, lecheniye i iskhody (Myocardial Infarction. Age Features, Treatment and Results). Diss. Sverdlovsk, 1957
Yasakova, O. I. In: *Voprosy kardiologii i revmatizma* (Problems of Cardiology and Rheumatism). Sverdlovsk, 1959, 72
Yasinovskaya, F. P. Aktivnost mekhanoretseptorov serdtsa v norme i pri eksperimentalnom infarkte miokarda (Activity of Cardiac Mechanoreceptors in Normal Conditions and in Experimental Myocardial Infarction). Moscow, 1966
Yater, W. M., Traum, A. H., Brown, W. G. *et al. Amer. Heart J.*, 1948, 36, 334; 1948, 36, 481; 1948, 36, 683
Yater, W. M., Welsh, P. P., Stapleton, J. F. *et al. Ann. Intern. Med.*, 1951, 34, 352
Yurenev, P. N., Alekseeva, T. A., Polotskaya, E. L. *Kardiol.*, 1964, 1, 9
Yurenev, P. N., Levina, S. I. In: *Nedostatochnost miokarda* (Myocardial Insufficiency). Moscow, 1966, 203
Yurenev, P. N., Semenovich, N. I. *Kardiol.*, 1970, 1, 16

Yuster, F. I. *Trudy Vsesoyuznoi konferentsii patologoanatomov* (Transactions of the All-Union Conference of Pathoanatomists). Moscow, 1956, 286
Zaitsev, V. M. *Kazansk. med. zh.*, 1961, 1, 68
Zakusov, V. V. *Farmakologiya nervnoi sistemy* (Pharmacology of the Nervous System). Leningrad, 1953
Zarubina, A. I. *Vrach. delo*, 1962, 2, 56
Zatuchni, J., Tom Tan K. *Circulation*, 1961, 23, 762
Zaus, E. A., Kearns, W. M. *Circulation*, 1952, 6, 593
Zelenin, V. F. *Sov. med.*, 1946, 7, 6
Zelenin, V. F. *Bolezni serdechno-sosudistoi sistemy* (Diseases of the Cardiovascular System). Moscow, 1956
Zenzinov, G. S. *Ter. arkh.*, 1949, 6, 65
Zhdanova, N. S. *Trudy 14-go Vsesoyuznogo s''ezda terapevtov* (Transactions of the 14th All-Union Congress of Internists). Moscow, 1958, 353
Zhdanova, N. S., Suvorova, L. V., Lesyuk, E. S. *Materialy 1-go Vserossiiskogo s''ezda kardiologov* (Proceedings of the First All-Union Congress of Cardiologists). Voronezh, 1968, 209
Zhuravlev, G. I., Schmidt, U. *Kardiol.*, 1968, 5, 25
Zilberman, D. B. *Kardiol.*, 1967, 1, 78
Zilberman, D. B., Krashennikova, N. G., Chechik, E. A. *et al. Klin. med.*, 1969, 1, 42
Zlochevsky, P. M. Voprosy diagnoza i prognoza ostrogo legochnogo serdtsa v aspekte elektrokardiologicheskikh issledovanii. (Problems of Diagnosis and Prognosis of Acute Pulmonary Heart from the Point of View of ECG Studies). Diss. Moscow, 1965
Zlotopolsky, A. R., Khazanov, A. I. *Klin. med.*, 1963, 5, 39
Zoll, P. M., Wessler, S., Schlesinger, M. J. *Circulation*, 1951, 4, 797
Zolotova-Kostomarova, M. I. Klinika i patologiya infarkta miokarda (Clinical Aspects and Pathology of Myocardial Infarction). Diss. Moscow, 1950
Zolotova-Kostomarova, M. I. *Tezisy dokladov nauchnoi konferentsii 2-go Moskovskogo meditsinskogo instituta posvyashch. XXII s''ezdu KPSS* (Theses of Reports to the Scientific Conference of the Second Moscow Medical Institute Dedicated to the 22nd CPSU Congress). Moscow, 1961, 14
Zolotova-Kostomarova, M. I., Stepanov, N. G. *Ter. arkh.*, 1958, 11, 3
Zuckermann, R. *Atlas der Elektrokardiographie.* Leipzig, 1955
Zuckermann, R. *Grundrisse und Atlas der Elektrokardiographie*, Leipzig, 1959
Zuev, V. N. *Sov. zdravookhr. Kirgizii*, 1961, 2, 23
Zysko, A. P., Kiseleva, Z. M., Serebrovskaya, U. A. *et al.* In: *Shok pri infarkte miokarda. Materialy konferentsii* (Shock in Myocardial Infarction. Proceedings of Conference). Moscow, 1960, 50
Zysko, A. P., Ruda, M. Ya., Rudneva, O. B. *et al. Ter. arkh.*, 1966, 3, 47

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The author works in a leading Moscow clinical hospital. In certain chapters he had the collaboration of Yu. M. Halperin and N. M. Baklykova of the Vladimirsky Regional Clinical Research Institute, Moscow.